IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK, et al., Plaintiffs, v. MYLAN PHARMACEUTICALS, INC., Defendant.	:	CIVIL ACTION NO. 09-184-LPS
MYLAN PHARMACEUTICALS, INC., Plaintiff, v. GALDERMA LABORATORIES,INC., GALDERMA LABORATORIES, L.P., and SUPERNUS PHARMACEUTICALS, INC., Defendants.	:	CIVIL ACTION NO. 10-892-LPS

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Wilmington, Delaware
Thursday, July 7, 2011
BENCH TRIAL - VOLUME C

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BEFORE: HONORABLE **LEONARD P. STARK**, U.S.D.C.J.

APPEARANCES:

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MORRIS NICHOLS ARSHT & TUNNELL, LLP
BY: JACK B. BLUMENFELD, ESQ.

and

Brian P. Gaffigan
Valerie Gunning
Official Court Reporters

APPEARANCES (Continued):

PAUL HASTING JANOFSKY & WALKER, LLP
BY: GERALD J. FLATTMANN, ESQ.,
CHRISTINE WILLGOOS, ESQ.,
JOSEPH M. O'MALLEY, JR., ESQ., and
MELANIE R. RUPERT, ESQ.
(New York, New York)

Counsel for Research Foundation of State University of New York, Galderma Laboratories, Inc., New York University, Galderma Laboratories, L.P., and Supernus Pharmaceuticals, Inc.

POTTER, ANDERSON & CORROON, LLP
BY: RICHARD L. HORWITZ, ESQ.

and

WILSON SONSINI GOODRICH & ROSATI, PC
BY: DAVID S. STEUER, ESQ.,
MATTHEW R. REED, ESQ., and
KIRIN K. GILL, ESQ.
(Palo Alto, California)

and

WILSON SONSINI GOODRICH & ROSATI, PC
BY: TUNG-ON KONG, ESQ.
(San Francisco, California)

and

WILSON SONSINI GOODRICH & ROSATI, PC
BY: LORI P. WESTIN, ESQ.,
(San Diego, California)

Counsel on behalf of Mylan Pharmaceuticals, Inc.

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P R O C E E D I N G S

(REPORTER'S NOTE: The following trial proceedings was held in open court, beginning at 9:05 a.m.)

THE COURT: Good morning, everyone.

Any issues anybody wishes to raise before I begin?

MS. WILLGOOS: There are a few objections that we'd like to take care of, your Honor.

THE COURT: All right. Your objections?

MS. WILLGOOS: Yes.

THE COURT: Go ahead. Come to the podium, please.

MS. WILLGOOS: Thank you, your Honor. There are two documents that we're objecting to the admissibility of. One is DTX-1014 that Mylan seeks to get in through the testimony of Robert Ashley. The document is an internal Supernus e-mail. Mr. Ashley was never a copy recipient or an author of the e-mail and he was never an employee and never -- was involved in any way with the e-mail chain, as he testified at the depositions. We object to that on lack of foundation and hearsay.

The second document is a Supernus e-mail, DTX-1085, and, again, they seek to get that through the testimony of Dr. Chang, who was neither a copy recipient nor

an author of the e-mail, and so we will also object to that on lack of foundation and hearsay, your Honor.

THE COURT: Excuse me. Is it your understanding that defendants intend to play more of the Ashley deposition or is he appearing live?

MS. WILLGOOS: No. They intend to play more of his deposition testimony as do we as part of our affirmative rebuttal case, your Honor.

THE COURT: All right. Thank you.

MS. WILLGOOS: Okay.

THE COURT: Let me hear from Mylan, please.

MR. KONG: Good morning, your Honor.

THE COURT: Good morning.

MR. KONG: Just to answer one logistical question, Mr. Ashley was deposed twice. So the first deposition was played. I believe the second deposition is intended to be played today.

To respond to the issues raised by Ms. Willgoos, would your Honor like to see the documents in question?

THE COURT: Sure. Could you pass those up?

MR. KONG: Sure.

(Mr. Kong handed documents to the Court.)

MR. KONG: So, your Honor, as to -- well, first of all, generally, both documents are e-mails exchanged between CollaGenex and Shire.

CollaGenex, if your Honor will recall, is the predecessor entity to Galderma, who was a plaintiff in one of the cases, a defendant in the other case. Shire is the predecessor to Supernus. So these are e-mails exchanged between two parties represented by counsel.

As to 1014, the document used with Mr. Ashley, that document records statements made by Mr. Ashley. As to the other document, it actually contains reference to the parameter they wanted to use, and both of these documents are relevant to the issue of the Chang patent and the proper inventorship of the Chang patent.

The other e-mail, 1085, I believe it is, references specifications that were used by -- requested by CollaGenex and used by Shire for purposes of formulation.

THE COURT: And what about the contention that they're hearsay?

MR. KONG: Well, it's our position that they're party admissions, your Honor.

THE COURT: All right.

MR. KONG: Thank you.

THE COURT: Thank you.

Ms. Willgoos, a response?

MS. WILLGOOS: Just briefly, your Honor. The fact that the parties are, in the e-mail exchange, are both

represented by counsel is irrelevant to the issue of whether there's proper foundation or whether the documents are hearsay.

And simply particularly for the Ashley document, DTX-1014, Mr. Ashley was not part of that e-mail chain, and so for both of these documents, there's lack of foundation and they are hearsay.

THE COURT: Is Mr. or Dr. Chang testifying by deposition?

MS. WILLGOOS: By deposition, your Honor.

THE COURT: Well, all right. Thank you.

I'm going to reserve ruling on the admissibility. We're going to hear the deposition testimony. I'm not sure at what point in the day you'll get to it. I will get you a ruling today on the admissibility of these two documents, but in the meantime, proceed in whatever order you wish, and we'll hear the testimony later if there's no objection to the testimony that's going to be played.

Anything else the plaintiff wishes to raise?

MS. WILLGOOS: Not at this time, your Honor.

THE COURT: Anything from the defense?

MR. STEUER: Your Honor, just quickly on a scheduling issue, late night communications suggest that we may close out the evidence today. We might do it before

6:00 o'clock. And if that's the case, I would propose that the parties come back tomorrow morning, if they have time left, to present closing arguments.

THE COURT: Any objection to that?

MR. O'MALLEY: No objection.

THE COURT: All right. That will be fine. And if you finish today, that's certainly fine as well.

I wanted to clarify, I don't think there's any confusion on this, but in terms of the briefing schedule, which I agreed to yesterday, I just want to make sure you all understand, to the extent there are objections that we are noting and not ruling on, which I think are only beyond the scope of the expert report, if you are going to renew those and brief those, that is to be done within those page limits that I agreed to yesterday. I don't want to see extra motions or extra briefing beyond what you all have proposed and I agreed to yesterday.

All right. If that takes care of all the issues, let's proceed with whoever the next witness is.

MR. REED: Thank you, your Honor. Mylan calls Dr. Werner Rubas.

THE COURT: All right.

... WERNER RUBAS, having been duly sworn as a witness, was examined and testified as

follows ...

THE COURT: Good morning, Dr. Rubas.

THE WITNESS: Good morning.

THE COURT: You may proceed.

MR. REED: Thank you, your Honor.

DIRECT EXAMINATION

BY MR. REED:

Q. Dr. Rubas, would you please introduce yourself to the Court.

A. Good morning. My name is Werner Rubas, and I'm from Redwood City, California.

Q. Are you here testifying as an expert witness on before of Mylan?

A. Yes, I am.

Q. And can you briefly describe your educational background?

A. I'm a pharmacist by training. I obtained my degree in Zurich from the Swiss Federal Institute of Technology in 1982. I also received a Ph.D. from the same institution in 1987.

Q. Tell us about your current job.

A. I'm the founder, president and CEO of a pharmacokinetic consulting company.

Q. Tell us just a little bit about that company.

A. The company is providing pharmacokinetic services to

the pharmaceutical and biopharmaceutical industry.

Q. And what positions did you hold prior to founding this consulting company?

A. After completion of my Ph.D., I had a teaching position at the Swiss Federal Institute of Technology. I assumed a post-doctoral fellowship in 1989 in Syntex in Palo Alto, California.

I progressed through my career from a scientist at Genentech to become a senior scientist at Core Therapeutics. I was recruited by a startup company as an associate director of pharmacokinetics at the end. I was working at Roche Palo Alto also as an associate director, pharmacokinetics.

Q. I appreciate you speaking close to the microphone, but that might be just a little bit too close.

Can you please describe your current involvement in academic organizations.

A. Sure. I'm on the advisory board of SPARK. SPARK is an organization at the medical institute of the Stanford University. The purpose of the SPARK program is to lead as academic research in the pharmaceutics with the industry.

Q. Can you tell us about your publications in pharmacokinetics.

A. Sure. I published approximately 50 papers. This includes numerous abstracts, peer-reviewed articles, book

chapters and review papers.

Q. Please describe your work as a peer reviewer of scientific manuscripts for potential publication in the pharmacokinetic field.

A. During the years of 1990, I was peer reviewing for a journal called Pharmaceutical Research. During that time, I reviewed numerous abstracts and articles that were submitted for publication.

Q. For about how long did you do that?

A. For about eight to nine years.

Q. Dr. Rubas, could you tell us about some accomplishments of yours that stand out in the field of pharmacokinetics.

A. Sure. When I was a post-doc at Syntex, we pioneered an absorption model called Caco-2 monolayers. This model became the industry standard to examine the potential for absorption for new drug entities.

I also successfully predicted a pharmacokinetic profiles of new drug ANDAs in animals and in human beings.

Q. Would you please look at Exhibit DTX-2194 in the binder in front of you, please.

A. Yes.

Q. Do you see that?

A. Yes, I do.

Q. What is that document?
A. This is my curriculum vitae.
Q. Is this an accurate summary of your educational and professional background?
A. Yes, it is.
MR. REED: I offered DTX-2194, your Honor.
THE COURT: Is there any objection?
MR. O'MALLEY: No objection, your Honor.
THE COURT: It's admitted.
(DTX-2194 received into evidence.)
MR. REED: Your Honor, we offer Dr. Rubas as an expert in the area of pharmacokinetic and pharmacokinetic modeling.
MR. O'MALLEY: No objection.
THE COURT: He is so recognized.
BY MR. REED:
Q. Dr. Rubas, what were you asked to do in this case?
A. I was given two questions regarding the pharmacokinetic properties of doxycycline in the context of the Chang patent.
Q. Have you prepared a slide summarizing your opinions?
A. Yes, I have.
Q. Will you please describe your opinions for us?
A. On this slide, I showed two opinions:
The first opinion is saying that prior to

April 2003, a person of ordinary skill in the art knew or could have known that a 40 milligram daily dose of immediate release doxycycline would provide steady state plasma concentrations of between .1 and 1 microgram per mil.

The second opinion here on the slide speaks to the fact that a person of ordinary skill in the art knew or could have known the ratio of immediate release to delayed release particles in a 40 milligram daily dose of doxycycline that would also provide a steady state plasma concentrations of between .1 and 1 microgram per mil.

Q. What did you consider in forming your opinions?

A. We summarized the resources that I considered. I understand the ordinary skill in the art. I used my own education and my professional experience. I reviewed numerous scientific papers. I applied legal principles.

I also reviewed documents produced by the parties, the expert opinions by the plaintiff as well as the Chang patent.

Q. Could you please briefly explain what the discipline of pharmacokinetics is?

A. Yes. Pharmacokinetics is the science that describes the time dependent change of the drug in an organism such as human beings.

Q. How is pharmacokinetics used?

A. Pharmacokinetics is used in many ways. In one way,

it's used to compare different compounds. It's also used to compare the same compound administered in different formulations, and it can also be used to create models and perform simulations.

Q. Is the word pharmacokinetics sometimes abbreviated PK?

A. Yes, it is.

Q. How do you measure or assess pharmacokinetic parameters?

A. You would have to administer a compound to a host organism, that could be an animal, that could be a human being. Over the time course of your experiment, you take multiple blood samples. You would estimate or you would determine the concentration of the drug in the blood samples and from the time plasma concentration time curve, you can extract pharmacokinetic parameters.

Q. Would you please give us some examples of pharmacokinetic parameters that can be measured?

A. Yes. This is a list that includes but is not limited to, for example, the plasma concentration. When the plasma concentration reaches the highest point, we call it a maximum concentration.

When we talk about a trough level or Cmin, that is usually at the end of the collection period or determined time period.

A drug exhibits a half-life which dictate how quickly that is exiting the system.

We also can extract the area under the curve, AUC.

Bioavailability can be estimated and several other parameters.

Q. What can a practitioner do with these pharmacokinetic parameters?

A. A practitioner will take these parameters and compare between different compounds, able to use these parameters as well as when the same compound is given a different administration or in different formulations or, as I mentioned earlier, I will use these parameters to perform simulations.

Q. Please tell us where a person of ordinary skill in the art will find these kinds of PK parameters?

A. This information is typically found in the scientific literature. If we are talking about commercialized products, then you will find the information in the label. You find it also in books such as the Physician's Desk Reference book which will list a lot of these parameters.

Q. In April 2003, what amount of information was known about doxycycline?

A. There was wealth of information regarding pharmacokinetics known for doxycycline. What I show on this

slide is there are five brand names on the market for doxycyclines, and the very first one was introduced in 1967.

There are numerous original articles that describe the pharmacokinetic properties of doxycycline.

There are at least a couple of review articles that have summarized and reviewed the prior -- the literature of the pharmacokinetics for doxycycline.

It was stated in these articles that doxycycline behaves in a dose linear fashion, and a biopharmaceutic classification system was also established before 2003 and the compound was classified as a class 1 compound.

Q. Would you please take a look in your binder at Exhibit DTX-2205.

A. I have in it front of me.

Q. What is this document?

A. This document is a review article written by Kenneth Agwuh and also Alasdair MacGowan.

Q. Is this an exhibit that you relied on in your opinions?

A. Yes.

MR. REED: I offer DTX-2205.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2205 received into evidence.)

BY MR. REED:

Q. And please turn to the next exhibit in your binder, DTX-2206 and tell us what is this document.

A. This document is another review article by Saivin and Owen.

Q. And did you rely on this document in forming your opinions?

A. Yes, I did.

MR. REED: I offer DTX-2206.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2206 received into evidence.)

BY MR. REED:

Q. Of the pharmacokinetic parameters of doxycycline available prior to April 2003, which did you look at in forming your opinions in this case?

A. Yes. So I go back to the slide that is available here. So I relied on the label for Periostat that was up there in 1998. And I also relied on the information in the Physician's Desk Reference book with represent to Monodox.

Q. What other public available information did you rely upon?

A. As we just discussed, there are numerous individual articles and review articles, and I relied on those as well.

Q. In addition to the pharmacokinetic properties that were known, what was known about absorption of doxycycline

prior to April 2003?

A. Here is a section of a paragraph from the review from Saivin, and what the review states here is after review in these original papers is the absorption primarily occurs in the duodenum.

Q. Now, have you heard the phrase "absorption window?"

A. Yes, I have.

Q. Is absorption window something a pharmacokineticist would consider when forming a drug?

A. Yes.

Q. In this case, did you know the absorption window of doxycycline?

MR. O'MALLEY: Objection, your Honor. Beyond the scope of his expert opinion.

THE COURT: The objection is noted.

You can answer.

THE WITNESS: I applied the information stated in this article.

BY MR. REED:

Q. Now, can you remind us what opinion you formed regarding immediate release doxycycline based on your work in this case?

A. My opinion is here on the slide, and it states that prior to April 2003, a person of ordinary skill in the art knew or could have known that a 40 milligram daily dose of

immediate release doxycycline would provide steady state plasma concentrations of between .1 and 1 microgram per mil.

Q. What methods did you use to come to the conclusion that this was predictable?

A. I used two methods. One method was a dose normalization method. The second one was a compartment modeling.

Q. Tell us what information you needed to know to be able to employ the first method, dose normalization?

A. I had to first establish that the pharmacokinetics of doxycycline was following a linear fashion.

Q. And why was that important?

A. That is important because if it would not follow a linear fashion, then my approach will be invalid.

Q. What does knowing that doxycycline specifically is dose linear allow you to do?

A. Once you have established the dose linear pharmacokinetic is in existence, then you can basically take the pharmacokinetic concentration at a particular dose, and when you double the dose, for example, then the concentration at that particular time point will also double.

Q. How did you use dose normalization in your pharmacokinetic modeling?

A. I applied this for my dose normalization, and I also

applied it for my compartment modeling.

Q. With respect to dose normalization first, what information did you use and how did you use it?

A. I show here on this slide the information provided in the label of Periostat. What we're looking here is a single 20 milligram dose of tablets. There is 20 individual, and I want to point out the highlighted column which indicates the maximum concentration which is here, 362 nanograms per mil plus or minus 101 nanogram per mil.

Q. And what did you do with that data?

A. So when you double the dose to 40 milligrams as an example, then you double the Cmax concentration, and we show the outcome at the bottom here, so when you doubled it to .362 microgram will basically become a .724 microgram per mil.

Q. How does that relate to your first opinion?

A. That relates to my first opinion that it was predictable to -- it was predictable that the 40 milligram immediate release doxycycline will stay between .1 and 1 microgram per mil.

Q. Did you perform a dose linear normalization with data from any other source other than the Periostat label?

A. Yes. I examined the literature provided by Malmberg and coworkers, and I did a dose normalization based on that data and I came to the same conclusion.

Q. Did you hear Dr. Rudnic's criticism of your use of mean data for tablets --

A. Yes.

Q. -- instead of capsules?

A. Yes.

Q. What data was available to you when you performed your work?

A. Tablet data.

Q. Did you use any capsule data in your work?

A. Yes. I used the capsule data from the Monodox.

Q. How did you use this Monodox capsule data?

A. The Monodox data in the Physician's Desk Reference book provides a table that lists the concentration at different time points and we showed this on the next slide.

The table here shows two rows. The top row here is the times. So blood samples were taken from the first one was .5 hours all the way out to 72 hours.

And on the bottom row, we see the concentration at the respective time point in microgram per mil, also from 30 minutes out to 72 hours.

Q. Can you describe the Physician's Desk Reference that you used to obtain this data?

A. This is a typical book that a physician in practice would consult to inform him or her what the pharmacokinetic properties of a particular drug would be. It has sometimes

this information. It has the Cmax in there. It has Tmax and whatever he needs to know to be sure that he provides the correct dose.

Q. And do you recall the year in which the particular version of the Physician's Desk Reference for Monodox used that you used?

A. I believe it was 1986.

Q. Would you turn to Exhibit DTX-2201, please.

A. I have it.

Q. Is this the Physician's Desk Reference that you relied upon?

A. Yes, it is.

Q. And what year is this?

A. 1997.

Q. So you remembered it wrong.

A. Okay.

Q. Is that right?

A. Yes.

MR. REED: Your Honor, I offer DTX-2201.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2201 received into evidence.)

BY MR. REED:

Q. Why did you select this data as the basis for building your pharmacokinetic model?

A. There were two primary reasons. Data provided here is dense enough that I can do my modeling.

Secondly, in reviewing the documents that I obtained from counsel from the plaintiffs, it became obvious that they also used this data set for their own modeling and simulation.

Q. Now, you are not talking about plaintiffs' experts; right?

A. No. I found this in the documents.

Q. From plaintiffs themselves?

A. Yes.

Q. Did you hear Dr. Rudnic criticize your use of mean data instead of individual data in your modeling?

A. Yes, I did.

Q. What data was available to a person of ordinary skill in the art in April 2003?

A. This is only the average data will be available to a person of ordinary art -- ordinary skill in the art.

Q. If individual data were available, how would you have used it?

A. If the individual data would have been available, I would also have created the geometric mean and would have done the same analysis.

Q. Okay. Referring now again to this Monodox data. How did you build your model?

A. First, I had to establish what kind of a compartment model Monodox is following. The principles that you apply is you plot the data that is listed in this table on a semilog plot, which means the concentration on the Y axis is in a logarithmic fashion whereas the time is in a linear, and the circles present the data out of this table.

What you then do is you look at basically the trend of line there the highest concentration to the lowest. When this trend line has only one slope, you establish that this is a one compartment model. I did the regression analysis, and you see there is a very high degree of confidence that this is a linear relationship between a coefficient, a variation coefficient of .989.

Q. What did you do next?

A. Once I know that this is a one compartment model and this was also confirmed in documents, I reviewed from the plaintiffs who concluded this is a one compartment model.

Then you apply a one compartment model and you fit the actual clinical data down here with a one compartment model and on this axis again, it's a semi-logarithmic plot. This is the concentration and this is the time. The red circles represent the actual data and the green line is the simulated plasma concentration.

And what it shows is that a one compartment model does well describe the pharmacokinetic or the plasma

concentration profile of Monodox.

Q. Now, how did you apply this model?

A. First, as I said, I had to establish that the pharmacokinetic follows a linear fashion. Then what you do is you take the information from this fitting and you apply a different dose. Then you simulate the pharmacokinetic, the plasma concentration profile as a different dose.

Q. What did you extract from this -- from the curved fit?

A. So important for a one compartment model is, for example, the volume of distribution, the elimination constant, linear absorption constant.

Q. Is the half-life another one of the parameters that you extracted?

A. Yes, the half-life is estimated from the down slope here, and the fitting program I used normally which is the standard, software package used in the industry gave me a. Half-life of 17 and-a-half hours.

Q. Did you hear Dr. Rudnic criticize your half-life of 17.5 hours?

A. Yes.

Q. How does this half-life that you calculated of 17.5 hours compare to the reported half-life of Monodox?

A. As a matter of fact, in the Physician's Desk Reference, which was just admitted, you can see in the table

that the reference listed a half-life of 16.33 hours. So I was actually having my fitting actually gives me a slightly longer half-life.

Q. Now, with respect to this model, you said that you used it to then simulate steady state; is that right?

A. That is correct.

Q. And is this depiction of the results of your simulation?

A. Absolutely. So this is the plasma concentration profile that I simulate for 40 milligram instant release dose of Monodox or doxycycline.

On the Y axis again is the concentration in microgram and on the X axis is the time.

I assumed five doses of 24 hours apart to reach steady state. And what you can appreciate from the simulated plasma concentration time profile is that at steady state, we are clearly below 1 microgram per mil and also at this minimum concentration, we are clearly above .1 microgram per mil.

MR. REED: Your Honor, I believe I omitted or I forgot to move for the admission of Exhibit DTX-2199, which is the Periostat labeled in which Dr. Rubas relied. And I offer that.

MR. O'MALLEY: No objection.

THE COURT: It is admitted.

(DTX-2199 received into evidence.)

BY MR. REED:

Q. Now, was all the information that you used in modeling and simulation available prior to April 2003?

A. Yes. I stated previously all the information was available information to generate the PK constants for the simulation came directly from the Monodox data. Other pharmacokinetic information was already cited in other different papers, including review articles.

Q. And based on the two different methods that you used, what opinion did you form regarding the steady state plasma concentrations of a 40 milligram daily dose of immediate release doxycycline?

A. My opinion is that prior to April 2003, a person of ordinary skill in the art knew or could have known that a 40 milligram daily dose of immediate release doxycycline will provide steady state plasma concentrations of between .1 and 1 microgram per mil.

Q. I would like now to switch to the second question that you were asked to form an opinion on. What opinion did you form regarding a 40 milligram dose of doxycycline that contains a combination of immediate release and delayed release portions?

A. My opinion is that prior to April 2003, a person of ordinary skill in the art knew or could have known the ratio

of immediate release to delayed release particles in a 40 milligram daily dose doxycycline that will provide steady state plasma concentrations of between .1 and 1 microgram per mil.

Q. How did you reach this conclusion?

A. I came to this conclusion again by examination of the available literature, and from the information provided in the various documents.

Q. How does the knowledge of absorption of doxycycline relate to your opinion?

A. The information in the literature was stating that the absorption occurs in the duodenum and that teaches me that a large portion of the compound has to be given in a manner that it is released and available for absorption by the duodenum.

Q. If a significant portion of doxycycline is not released immediately, what would you expect?

A. I will be -- I will expect that it would not be absorbed.

Q. What support did you find for your conclusion?

A. By reviewing the patent application filed by Robert Ashley. I took out this paragraph, and I highlighted the conclusion that supports or corroborates what I thought is that it is preferred that at least 50 percent, more preferably greater than 80 percent of the tetracycline in

the composition be released in the upper GI tract.

MR. O'MALLEY: We'll just object beyond the scope of the expert opinion.

THE COURT: It is noted.

BY MR. REED:

Q. How is this information relevant to your opinion?

A. Again, as I mentioned early, it teaches me that a combination formulation of instant release and not instant release has to be fabricated in a manner that a significant portion of the drug is in the instant release portion.

Q. Did you create a pharmacokinetic model to reach your conclusion about the immediate release portion?

A. Yes, I did.

Q. Can you please describe what we see here?

A. This slide shows a modeling simulation which is based on the pharmacokinetic model that I prepared earlier for the instant release. This graph shows, again, on the Y axis the concentration and in micrograms per mil, and on the time axis, X axis, I have the time, and again I simulate out to five individual doses given of 24 hours apart.

Each dose level is depicted in a different color. I have 20 milligram instant release as green, the 25 is blue, 30 milligram is red, and the 40 milligram is in black.

Well, you can appreciate from this graph is that

when you need a minimum of 25 milligram provided as an instant release to be certain that your minimum concentration stays above the .1 microgram per mil.

Q. In terms of meeting the plasma concentration goal or target of between about.1 microgram per mil to 1.0 microgram per mil, can you get better results from your simulation with a dose higher than --

A. Absolutely.

Q. Dr. Rubas, let me finish that question, please.

(Continuing): -- better results from your simulation with a dose higher than 25 milligrams of doxycycline in an immediate release form?

A. Absolutely. As you can appreciate from this figure here, the red line, which is the 30 milligram, gives you a better certainty that you stay above the .1 microgram per mil and while not exceeding the 1.0 microgram per mil level.

MR. REED: Thank you, Dr. Rubas.

No further questions at the time.

THE COURT: Cross-examination.

MR. O'MALLEY: Your Honor, Joe O'Malley for Galderma.

If I may proceed.

THE COURT: You may.

MR. O'MALLEY: I'd like to hand out some books. If I may approach?

THE COURT: You may.

(Binders passed forward.)

CROSS-EXAMINATION

BY MR. O'MALLEY:

Q. Good morning, Dr. Rubas.

A. Good morning.

Q. Did I pronounce that correctly, by the way?

A. Yes, you did.

Q. Dr. Rubas, your basic opinion is that Dr. Chang's solution to the formulation problem he was presented with was not surprising in 2003; correct?

A. My opinion is that the concentration was predictable.

Q. So your opinion is that the use of an IR/DR combination formulation to achieve the blood plasma levels of his claims was not surprising in 2003; is that fair?

A. As I said, all the information is available in the literature.

Q. So you agree with me, that is basically a summary of your opinion?

A. No.

Q. You disagree? It was not surprising?

A. It was not -- as I said, it was predictable based on the pharmacokinetic information that a person of ordinary skill in the art could find in the public domain.

Q. And I'm just trying to determine what it is that was

not predictable, see if we can agree on that as a premise. What you are basically saying is that the use of IR and DR in combination, as in Dr. Chang's claims, was not surprising in 2003 to achieve the blood levels that are claimed in his patent. Is that fair as a starting point?

A. Yes.

Q. Now, Dr. Rubas, are you aware that Galderma's Oracea product employed Dr. Chang's patented invention?

A. No.

Q. You are not aware of that. And were you aware Galderma's Oracea product has garnered hundreds of millions of dollars of sales since its launch?

A. No.

Q. Now, by contrast, Dr. Rubas, if you totalled sales of all the controlled release formulations that you developed that made it to the market in the United States, what would that total be?

A. I have not developed any modified release formulations.

Q. You have not developed any modified release formulations that have made it to the market in the U.S.?

A. Worldwide.

Q. Worldwide. And just for the court reporter, it will be better if we don't speak over one another.

And you have been in this field for over

25 years; is that correct?
A. Yes.
Q. Now, in forming your opinions that it would not have been surprising at the IR and DR combination that Dr. Chang employed would meet his claimed plasma concentration ranges, you employed a hindsight analysis; correct?
A. I disagree.
Q. Well. For example, you weren't asked, when presented with the formulation problem that Dr. Chang was presented with and had nothing but your own knowledge in the prior art to put towards that problem, how would you solve it. Mylan didn't ask you that question; correct?
A. Counsel gave me all the parameters that I used to form my opinion.
Q. But they didn't ask you the question I just posed to you; correct?
A. Counsel asked me to provide pharmacokinetic predictions of a 40 milligram immediate release and a combination of immediate release and delayed release formulation and to predict whether or not such a formulation would stay between .1 and 1 microgram per mil at steady state.
Q. So they didn't, in other words, say if you were going to formulate a controlled release formulation of doxycycline as a method of treating rosacea in 2003, with just the prior

art and your own knowledge, how would you go about it? I'm just trying to determine is it correct Mylan never asked you that question?

A. As I just stated, I got that question from counsel with all the parameters.

Q. And the question you received from counsel was not the question I just posed to you; fair enough?

A. Yes.

Q. Instead, as you put it, you were given some of the basic parameters of Dr. Chang's claims and you were asked, looking backwards to 2003, was Dr. Chang's solution surprising; correct?

A. No.

Q. No. Well, let's take a look at the question that you were asked. And let's pull up Dr. Rubas's report, paragraph 1. It should be in that notebook I just handed to you.

Do you see a copy of your expert report in there, sir?

A. Yes.

MR. O'MALLEY: Now let's pull up the latter half of paragraph 1.

BY MR. O'MALLEY:

Q. Let's start with the latter sentence there. You were asked basically two questions as you put it; right?

A. Yes.

Q. And the second question you were asked was, for your opinion as to whether a person of ordinary skill in the art in 2003 could have predicted a ratio of instant release versus delay release multi-particulates that would also have provided steady state plasma concentrations of doxycycline that stay between about .1 and 1.0 micrograms per milliliter.

Correct?

A. Yes.

Q. And you understand, you had read, as you testified, Dr. Chang's patent prior to presenting your opinions; is that correct?

A. Yes, I read it.

Q. And you understand that Dr. Chang's claims include, among other things, a ratio of instant release versus delayed release multi-particulates; is that correct?

A. Yes.

Q. And you know from reading Dr. Chang's patents that that combination is claimed to provide a steady state plasma concentration of doxycycline that stays between about .1 micrograms per milliliter and about 1.0 micrograms per milliliter; is that correct?

A. Yes.

Q. So you recognize those are parameters of Dr. Chang's claims that were provided to you as the starting point for

your analysis; is that correct?
A. I'm not exactly sure where counsel got the parameters from.
Q. Didn't you just tell me you recognized those to be parameters of Dr. Chang's claims?
A. I do, but counsel might have gotten these parameters from somewhere else.
Q. That, coincidentally, might have been also parameters of Dr. Chang's claims?
A. I cannot speculate. I don't want to speculate.
Q. But, in any event, these parameters, whether they came from another source in addition to Dr. Chang's claims were the starting point for your analysis; is that correct?
A. Yes.
Q. And you worked from there?
A. Yes.
Q. Okay. Now, you did not conduct any independent evaluation yourself of what a person of ordinary skill in the art would have done in 2003 absent those parameters we just looked at that were provided to you by counsel; is that correct?
A. Correct.
Q. And you did not consider whether a person of ordinary skill in the art in 2003 would have even been motivated to design a combination of the immediate release and delayed

release formulation to begin with to accomplish the claim plasma concentration parameters; correct?

A. I don't understand why this is relevant.

Q. But you didn't consider it; correct?

A. Correct.

MR. O'MALLEY: No further questions, your Honor.

THE COURT: All right. Any redirect?

MR. REED: Yes. Maybe just a couple of questions, your Honor.

REDIRECT EXAMINATION

BY MR. REED:

Q. Dr. Rubas, I believe you said that you did not confirm where the many parameters came from, that you were supplied by counsel; is that right?

A. Yes. I did not follow up where they exactly were coming from.

Q. Do you have an understanding of where counsel got those when they gave them to you?

A. I understand they come from the Ashley patent.

MR. REED: No further questions, your Honor.

THE COURT: All right. Thank you. You may step down, Doctor.

(Witness excused.)

THE COURT: Mylan may call its next witness.

MR. REED: Mylan calls Dr. David Friend, your

Honor.

THE COURT: All right.

... DAVID R. FRIEND, having been duly sworn as a witness, was examined and testified as follows ...

THE COURT: Good morning, Doctor.

THE WITNESS: Good morning.

(Mr. Reed handed a notebook to the witness.)

DIRECT EXAMINATION

BY MR. REED:

Q. Good morning, Dr. Friend. Would you please introduce yourself to the Court.

A. Yes. My name is David Friend. I am originally from California, but over the past few years I've been taking the sojourn on the East Coast.

Q. Are you here testifying as an expert on behalf of Mylan?

A. Yes, I am.

Q. Could you please summarize your education for the Court.

A. Yes. I have a biochemistry degree from the University of California at Davis in 1979. Did a Ph.D. degree from University of California, California at Berkeley, in chemistry.

Q. What did you do after you received your doctoral

degree?

A. I took a position at the Stanford Research Institute, also known as SRI International, in Menlo Park, California, where I worked for ten years on a range of drug delivery systems, including oral controlled release dosage forms.

Q. What did you do after your ten years at SRI?

A. I joined a company called Cibus Pharmaceutical, where I eventually became the chief scientific officer and was in charge of developing a wide range of oral dosage forms for controlled release into the gastrointestinal tract.

Q. Can you briefly describe the other positions that you have held through the course of your career?

A. Yes. I've had several other positions, including drug device combination work. I have a position with Elan as a senior formulation director, where I developed some pH independent post-release dosage forms for use in the gastrointestinal tract, and most recently I've been employed at Conrad.

Q. Can you tell us a little bit about your current position at Conrad?

A. Yes. Conrad is a division of the OB/GYN department at Eastern Virginia Medical School, and we are funded to develop new ways to prevent the transmission of HIV to women who live in the developing world.

My job is to be head of product

development, where I'm involved with all aspects of taking the drug substance through reformulation, formulation, scaleup, manufacturing, including up to Phase III clinical trials.

Q. What laboratory research have you conducted during your career?

A. Very wide range of laboratory research in the area of drug delivery. It encompasses almost all sorts of dosage forms. Oral controlled release, delayed release, targeting of drugs to the lower G.I. tract, to treat inflammatory bowel disease, transdermal systems, including gels and patches, electronic systems, thin films for oral dosage forms, dry powder inhalers and most recently intravaginal rings for sustained release of microbicides.

Q. Can you please describe your publications?

A. Yes. I have about 170 publications split roughly evenly between peer-reviewed research articles and abstracts and including several book chapters.

Q. Please describe your role as an editor and as a peer reviewer for scientific journals.

A. Yes. I was for about five years editor of the Journal of Controlled Release, the U.S. editor. I've also sat on a number of editorial boards for medical and pharmaceutical journals. And most recently, I'm a member of the editorial board of Drug Delivery and Translational

Research.

Q. Please describe your activities as a member of professional organizations.

A. Yes. I'm a member of the Controlled Release Society, AAPS, American Association of Pharmaceutical Scientists. I've also been involved in organizing symposia, mini symposia, workshops on a variety of topics over the years, both nationally and internationally.

Q. Would you please look in your witness binder at Exhibit DTX-2128.

A. Yes.

Q. Can you tell us what that document is?

A. It's my curriculum vitae.

Q. Does it accurately summarize your educational and professional experience?

A. Yes, it does.

MR. REED: Your Honor, I offer DTX-2128.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2128 was admitted into evidence.)

MR. REED: Your Honor, also at this time we offer Dr. Friend as an expert in the field of designing and developing controlled release drug delivery systems.

MR. O'MALLEY: No objection.

THE COURT: He's so recognized.

BY MR. REED:

Q. Dr. Friend, what were you asked to do in this case?

A. I was asked to form an opinion concerning the Chang patent.

Q. Can you please summarize the opinion you formed in the case?

A. Yes. I formed four opinions. The first is that the Ashley '932 application, which was available prior to April 2003, anticipates the asserted claims of the Chang patent.

Secondly, that the claims of the Chang patent are obvious in view of prior art available prior to 2003.

And, thirdly, the Chang patent specification lacks written description to support the narrow range of plasma concentrations that are required by claims 4 and 18.

And then, fourthly, there is a lack of evidence that Mylan's proposed generic formulation will infringe claims 4 and 18 of the Chang patent.

Q. In addition to the Chang patent, what else did you consider in forming your opinions?

A. In addition, I reviewed the Chang patent file history and other documents that were produced for me. I applied the understanding of one of ordinary skill in the art, the

Court's claim construction, applicable legal principles, prior art references, plaintiff's experts' opinions, my own education, experience and knowledge.

Q. And can you please describe the asserted claims of the Chang patent.

A. Yes. There are asserted claims 1 through 5, 7 through 9, 13 through 21. The overall structure of the asserted claims are based on claim 1, 15 and 20. These are independent claims. And each have associated dependent claims. For example, claim 13 is dependent on claim 2, which is dependent on claim 1. And I will go through this in some more detail in a moment.

Q. What do the three independent claims have in common?

A. They have in common, with the exception of a short preamble, which in the case of claim 1 is composition 15, a method of treatment, and 20, a process for preparing, they are virtually identical in that they claim an oral once daily dosage of doxycycline, steady state plasma concentrations of between 0.1 and 1.0 micrograms per ml, immediate release portion of about 30 milligrams doxycycline, delayed release pellets of about ten milligrams doxycycline, coated with an enteric polymer, and one or more pharmaceutical excipients.

Q. What are the additional elements of the dependent claims?

A. Those can be summarized here. The immediate release portion is actually in the form of a pellet. These pellets are found in a capsule. There is a narrower steady state plasma concentration claimed of 0.3 to 0.8 micrograms per ml. The excipients are further broken down into classes, and then, finally, the proportion of IR and DR pellets is claimed.

Q. Backing up half a step to talk a little more generally, can you tell us, what is a controlled release dosage form?

A. A controlled release dosage form is a dosage form that can accomplish a number of functions targeting, and I will just restrict this to oral delivery, where typically it encompasses sustained or prolonged release, delayed release, and those are the two primary forms of controlled release for oral delivery.

Q. Why would someone of ordinary skill in the art incorporate a drug into a controlled release dosage form?

A. Well, I think we've heard already that with the sustained release system, it reduces the number of doses required over a given period of time. This improves patient compliance and should improve therapeutic outcome.

Secondly, there's a scientific rationale often used, and that's that the plasma concentration ranges can be

better controlled, such that the plasma concentrations don't rise above a certain point, perhaps leading to toxicity or fall below a certain level where efficacy would be lost.

Q. How would a pharmaceutical formulator have made a controlled release dosage form in April 2003?

A. Well, a formulator would have, at his or her disposal, a range of technologies available through a number of what we call drug delivery companies.

Q. What are some of those technologies that were available?

A. Well, those technologies were associated with certain companies. Elan, where I was employed for awhile, has a technology called SODAS and IPDAS. Eurand has Diffucaps, and Ethypharm has a similar multi-particulates with dosage form, as well as other organizations.

Q. What is multi-particulate controlled release technology?

A. That's a technology quite common now these days where multiple beads or pellets are used wherein the drug can be located in the core or sprayed onto or applied to the external portions of a sugar bead, and then additional multiple layers can be added to provide more functionality to those units.

Q. Was multi-particulate controlled release technology available in April 2003?

A. Yes, it was widely available.

Q. Did you create a slide showing different drug release profiles?

A. Yes, I did.

Q. Now, this isn't your handwriting, is it?

A. No. No. I did not draw this. This is taken, reproduced from the Ashley '854 application, and it's similar to the slide shown by Dr. Rudnic earlier. This just happens to be I think the first version, a hand-drawn version. And it does demonstrate, interesting enough, several drug release profiles.

The difficulty with this figure is that it shows those profiles indirectly. What it shows is the resulting plasma concentrations that may be obtained from instant release dosage form or a sustained release or a delayed release preparation.

The difficulty with this is that in between the time the drug is released in the gastrointestinal tract and the time course for its appearance in plasma can vary tremendously from drug to drug.

MR. REED: Now, your Honor, I offer DTX-1008.

THE COURT: Is there any objection to DTX-1008?

MR. O'MALLEY: No objection, your Honor.

THE COURT: It's admitted.

MR. REED: Thank you.

(DTX-1008 was admitted into evidence.)

BY MR. REED:

Q. You mentioned available technologies for multi-particulate controlled release formulations. What are some examples of commercial formulations that were available prior to April 2003 and that used multi-particulate technology?

A. Actually, a fairly wide range of drugs were available in multi-particulate controlled release technologies. Ritalin is one from Eurand. Cardizem CP for controlled hypertension. Over-the-counter products, such as Vitamin C is available. Narcotic analgesics, non-steroidal anti-inflammatory drugs. Essentially a wide range of drugs with various physical and chemical properties.

Q. And those were all available prior to April 2003?

A. Yes, those were all available.

Q. You understand that Shire Pharmaceuticals, which later was named Supernus, was hired by CollaGenex, which later became Galderma, to help develop Oracea; is that right?

A. Yes.

Q. Did Shire in April 2003 already have any commercially available products using a multi-particulate based technology?

A. Yes. It's my understanding that two products were

available prior to that time. One, Carbatrol, and the other, Adderall XR.

Q. What was the name of Shire's multi-particulate technology?

A. Microtrol.

Q. Okay. Now let's go over your first opinion.

What is the first opinion you formed about the validity of the Chang patent in view of the available prior art?

A. That it was anticipated by the Ashley '932 application.

Q. Can you tell us what you did to form your opinion?

A. Yes. I applied the information that was -- that I believe was available to one in the field and the reading in detail of the '932 application.

Q. Did you consider the Court's claim construction?

A. I certainly did, yes.

Q. Did you follow this same general procedure for each of your opinions that you offered today?

A. Yes, I did.

Q. Now, the prior art reference that you concluded anticipates the Chang patent was what?

A. Ashley '932. It was published in October of 2002, filed originally internationally on the 5th of April 2002, and it claims a priority date back to the fifth of April of

2001. The inventor is Robert Ashley, and it generally addresses methods of treating acne.

MR. REED: Your Honor, I offer Exhibit DTX-2111.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2111 was admitted into evidence.)

BY MR. REED:

Q. Please describe the teachings of the '932 application in general terms.

A. In general terms, it's an application that outlines the use of tetracycline compounds to treat acne rosacea specifically, and it describes various oral dosage forms, as shown in the second box below.

Q. What does the Ashley '932 application say about controlled release technology?

A. Well, in addition to the information disclosed in that application, it has further reference to a patent application called -- entitled Controlled Delivery of Tetracycline and Tetracycline Derivatives. This was filed on April 5th, 2001 by CollaGenex, and the application, the aforementioned application is incorporated herein by reference.

Q. Have you reviewed the patent application filed on April 5th, 2001, that is referenced in this paragraph?

A. Yes, I have.

Q. What relationship exists between the Ashley '932 application and the application that is incorporated by reference?

A. It includes the fact, has the same assignee, CollaGenex, the same inventor, and most tellingly, it was filed on the same day as the '932 application.

Q. Okay. Let's take a look at this other application.

Is this the other application that was incorporated by reference?

A. Yes, it is.

MR. REED: Your Honor, I offer DTX-1008.

MR. O'MALLEY: No objection, your Honor.

THE COURT: It's admitted.

(DTX-1008 was admitted into evidence.)

BY MR. REED:

Q. Can you describe the '854 patent in general terms?

A. Certainly. In general terms, it focuses on delivery methods of tetracycline to a host, and it describes various controlled release formulations and approaches that would lead to plasma concentrations that would be absent of any anti-microbial activity.

Q. Given the incorporation by reference in the '932 application of the '854 application, do you consider the teachings of the '854 application related to the controlled release of tetracyclines to be part of the '932

application?
A. Yes, I do.
Q. Now, did you compare the Ashley '932 application to claim 1 of the Chang patent?
A. Yes, I did.
Q. Did you prepare a table to help describe the comparison you made?
A. Yes.
Q. Can you describe the table for the Court and generally what it contains?
A. Certainly. Very briefly, on the left, in this case, this example, we're examining claim 1 of the Chang patent, and I've broken down that claim into various elements to better compare with the '932 application.

On the right, we have the citation of, the disclosure of that element of the claim, Chang patent.
Q. Can you describe, please, what we learned from the '932 application regarding oral administration.
A. Certainly. The first element of the Chang, claim 1, is that the oral pharmaceutical composition, that would be an oral form, and we find that in Ashley '932, page 14, that the application discloses that the tetracycline compound is administered orally.
Q. What do we learn regarding doxycycline?
A. We learn that, again, in the '932 application of

Ashley, on Page 16, that the tetracycline is specifically doxycycline.

Q. What do we learn regarding once daily?

A. It's found also in the '932 application, where, on page 15, it's stated that the tetracycline compound may be administered one to six times a day, and more preferably one to four times a day. Hence, the once-a-day disclosure.

Q. What do we learn regarding the steady state blood levels of claim 1?

A. Well, there are actually two locations. The '932 application, first on page 10, it states that the doxycycline is administered in an amount which results in a serum concentration of about 0.1 and 0.8 micrograms per ml.

And in the '854 application on Page 5, the range is stated to be 0.1 and 1.0 micrograms per ml, the same as in the Chang patent.

Q. What do we learn regarding the immediate release and delayed release portions of doxycycline?

A. Well, we learn, first of all, that the total dose of doxycycline is 40 milligrams, and that's found on the Ashley application, '932, page 15, second-to-the-last line there.

And then it refers to further information on ways to deliver the tetracycline in the '854 application.

Q. And what do we learn about the combination of instant release and delayed release?

A. Well, in the case here, '854 states that the composition can include from a group consisting of instantaneous release and delayed release agent and combinations thereof.

Q. What do we learn about pellets?

A. Pellets are found in the '854 application when the dosage forms are described as alternatively being a solid form, such as, among other things, a pellet.

Q. What do we learn about the ratio of the immediate release and delayed release portions of doxycycline?

A. Okay. In the '854 Ashley application, on page 16, it states that the preferred amount of drug release be at least 50 percent and more preferably greater than 80 percent that should be released in the upper gastrointestinal tract. And this range includes in percent terms the about 75 percent to 25 percent of immediate release.

Q. What do we know about formulating a 40 milligram total dose with about 30 milligrams of immediate release and about 10 milligrams of delayed release doxycycline?

A. We know that the amounts of immediate release, according to Dr. Rubas's report, that that amount of immediate release to delayed release can be no less than 25 milligrams. And as he also pointed out, and I agree with his opinion, that that would be unacceptably too close to be practical and that the ratio would be more preferably

75 percent or 30 milligrams in about 25 percent or about 10 milligrams.

Q. What do we learn from the '932 application regarding the enteric coating on the delayed release pellets?

A. The use of enteric coatings is commonly known and also disclosed in the Ashley application where examples of delayed release agents are provided, and these include polymer or biodegradeable coatings, and this would include enteric coatings.

Q. What do we learn about excipients?

A. Excipients are found -- examples of excipients are found throughout the '932 and '854 application, but I just listed one example here where, pharmaceutically acceptable additional ingredients. In other words, excipients are provided for.

Q. In sum, what is your opinion regarding claim 1 of the Chang patent in light of the '932 application?

A. It is my opinion that the '932 application anticipates claim 1 of the Chang patent.

Q. Is that your opinion even though the '932 application does not recite the numbers 30 milligrams and 10 milligrams for the immediate release and delayed release portions doxycycline?

A. Yes.

Q. Why?

A. Well, because the required target range of 0.1 to 1.0 micrograms per mil as stated in the '932 application requires a very narrow range of ratios that can accomplish and reach that target goal. This narrow range of ratios necessarily encompasses the amount of about 75 percent immediate release and about 25 percent delayed release. And in terms of milligrams, that would be about 30 milligrams IR and about 10 milligrams DR.

THE COURT: Dr. Friend, I would ask you to push the microphone away just a little bit.

Thank you.

BY MR. REED:

Q. Does the Ashley '932 application anticipate any other asserted claims of the Chang patent?

A. Yes.

Q. Which ones?

A. The remaining asserted claims.

Q. All of them?

A. All of them.

Q. Did you prepare a table to help explain your opinions regarding the rest of the asserted claims?

A. Yes.

Q. Let's take a look first at claim 2.

Please describe your anticipation opinion regarding claim 2.

A. Yes. Claim 2 is dependent on claim 1 with the restriction that the immediate release portion is in the form of pellets. And in the '854 application, pellets are described on page 12. So for this reason, it is my opinion that claim 2, also with respect to what I already provided an opinion on claim 1, is anticipated.

Q. Let's turn to claim 3.

A. Okay.

Q. What is your anticipation opinion regarding claim 3?

A. Here we have the pellets are contained in a capsule. And in '854, this is stated quite clearly, polymeric capsules filled with solid particles. And so based on this clear statement, it is my opinion, as well as the reasons I provided for anticipation of claims 2 and 1, I believe claim 3 is anticipated by '932.

Q. Please describe your anticipation opinion regarding claim 4.

A. Claim 4 is directed towards the narrower steady state plasma concentrations and disclosures of these ranges are found in both '932 and '854. And this includes the range more preferably 0.4 and 0.7 micrograms per mil and, '854, 0.3 and 0.8 micrograms per mil.

Therefore, my opinion is that claim 4 is anticipated by '932 and, for the reasons I have already provided for my opinion regarding claim 1, I believe claim 4

is anticipated by the '932 application.

Q. Please describe your anticipation opinion regarding claim 5.

A. Yes. Claim 5 is directed now more at a narrower range of excipients as defined by function; that would be a binder, a disintegration agent, filling agent, so on and so forth. Excipients defined as such in the '932 application can be found as shown in the box below. Pharmaceutically acceptable additional excipients such as stabilizers are included.

It is for this reason, the statement that I believe claim 5, and for the reasons I already stated about claim 1, that claim 5 is anticipated by the Ashley '932 application.

Q. Please describe your anticipation opinion regarding claim 7.

A. Yes. Claim 7 now gets further down into different types of excipients specifically naming various agents, in this case, disintegrating agents consisting of a group of corn starch and others; and in the '932 application, we find corn starch mentioned. Therefore, it's my opinion that the '932 application anticipates this claim and in light of also the fact that the reasons I have given above for claim 1 that it's anticipated.

Q. Please describe your anticipation opinion regarding

claim 8.

A. Eight regards now or focuses on filling agents consisting of the group among others lactose. Lactose is found in the '932 application on page 15. And for this reason, I believe, in addition to the reasons I gave for claim 1 being anticipated, I believe claim 8 is anticipated by the '932 application.

Q. Please describe your anticipation opinion regarding claim 9.

A. Claim 9 refers to surfactants consisting from a group including sodium laurel sulfate, and sodium laurel sulfate is identified in the '854 application highlighted here in yellow on page 14. For this reason, I believe the '932 application anticipates claim 9 and for the reasons claim 5 I gave above earlier for claim 5. So this is the basis for my opinion concerning anticipation of this claim.

Q. Please describe your anticipation opinion regarding claim 13.

A. Okay. Claim 13 is dependent on claim 2. Here, we have a change in the ratio expressed as percent as opposed to previously milligrams where the immediate release portion constitutes about 80 percent to about 70 percent total pellets in a composition. And for the reasons that I provided concerning the ratios of immediate release to delayed release for claim 1, it follows then that claim 13

as well as claim 2 are anticipated by the '932 application.

Q. Please describe your anticipation opinion regarding claim 14.

A. Okay. Claim 14 is dependent on 13. Here, we have a statement of the immediate release portion expressed as a percent rather than a milligram, so about 75 percent of the total pellets in the composition, and the arguments I provided for the basis of my opinions for reasons I gave for claim 1 apply directly here. So I believe that the '932 Ashley application anticipates this claim as well.

Q. Now, this slide, DDX-635, deals with all the asserted claims that depend from claim 1; is that right?

A. Yes.

Q. There, the next asserted claim is claim 15. An independent claim. Would you please describe your anticipation opinion regarding claim 15?

A. Yes. Claim 15, an independent claim, is focused or directed towards a method of treating rosacea. And '932 application provides the following information I highlighted in yellow just to save time and not read it. But the invention provide a method of treating acne in a human, and various forms of acne. Ultimately acne, rosacea being identified towards the bottom of that paragraph.

Q. And based on that, what is your opinion with respect to claim 15?

A. My opinion is that claim 15 is anticipated by the Ashley '932 application.

Q. And is that for all the same reasons as you described with respect to claim 1?

A. Yes.

Q. Please describe your anticipation opinion regarding claim 16.

A. Claim 16 is dependent on 15, and here it states that the mammal is specifically a human. And in '932, on page 5, it states that the method of treating acne is in deed directed towards a human and for this reason I believe that claim 16 as well as for the reasons I stated for claim 15, that this claim is anticipated by the '932 application.

Q. Please describe your anticipation opinion regarding claim 17.

A. 17 is similar to claim 3 above where the pellets and the composition are contained in a capsule, and I applied the same reasoning that I did for claim 3, that this was disclosed in the '932 application, and also for the reasons I provided above for claim 15, therefore, claim 17 is anticipated by the '932 application.

Q. Please describe your anticipation opinion regarding claim 18.

A. Claim 18 is parallel to claim 14 in that the steady state blood levels are defined as being between 0.3 and

0.8 micrograms per mil. For the reasons I gave for the anticipation of claim 4 above, as well as 1, there, I conclude it's my opinion that claim 18 is anticipated by the '932 application.

Q. In your answer I think at one point I think you referred to claim 14. Did you mean to refer to claim 4?

A. 15. 15. Excuse me.

Q. We were talking about claim 18, and I think you said it's parallel to claim 14.

A. Claim 4. Claim 4.

Q. Thank you. Can you please describe your anticipation opinion with respect to claim 19?

A. Yes. Here we're back to excipients again, a similar list as we found in claim 5 above. And for the reasons I provided that claim 5 was anticipated by '932, the same reasoning, it forms my opinion that it is anticipated by the '932 application.

Q. Please describe your anticipation opinion regarding the next independent claim, claim 20.

A. Okay. This claim is again very similar to 1 and 15 with the exception of the preamble. And here, the claim is a process for preparing an oral pharmaceutical composition.

And the preparation of pharmaceutical products of this type is found in '932, on page 14, where it indicates that tetracycline compounds can be formulated as

understood by practitioners in the art of the and these preparations can be made according to conventional methods. For this reason, I believe or it's my opinion that claim 20 is anticipated by the '932 Ashley application.

Q. And for all the same reasons you offered with regard to claim 1 as well?

A. Yes.

Q. Please describe your anticipation opinion regarding claim 21.

A. Claim 21 is dependent on claim 20. And it states more this range of types of excipients binders, disintegrating agents and so on. And for the reasons I provided in claims 5 and 19, the same reasons apply, it's my opinion that this claim as well as the reasons that I provided for claim 20, this claim is anticipated by the '932 application.

Q. In sum, is it your opinion that all of the asserted claims of the Chang patent are invalid as anticipated by the '932 application?

A. Yes, that's my opinion.

Q. Let's move to the second of your opinions. What is the second opinion you formed?

A. The second opinion is that the claims of the Chang patent are obvious in view of the prior art available in the year 2003.

Q. Does this apply to all the asserted claims of the Chang patent?
A. Yes, it does.
Q. On which prior art do you base your obviousness opinion?
A. I rely on three obviousness references. One, Ashley '932 application, standing alone; and then Ashley '932 combined with U.S. patent '304; and, thirdly, the '932 Ashley application combined with U.S. patent ending '819.
Q. So each of these are three different obviousness opinions; is that right?
A. That's correct.
Q. Let's take your first obviousness opinion. Does this opinion reflect a combination of references?
A. No, it does not.
Q. What is the basis of your opinion that the '932 application renders obvious all asserted claims of the Chang patent?
A. Well, firstly, for all the reasons that I provided under anticipation, and as applied to those reasons, applied as an obviousness, it's for the same reason Ashley '932 makes all the asserted claims of the Chang patent obvious.
Q. Did you combine your understanding of the background, knowledge available to a person of ordinary skill in the art in April 2003 together with the '932 application?

A. Yes, I did.
Q. Can you describe the knowledge that was in possession of a person of ordinary skill in the art in April of 2003?
A. Yes. I did. And with transport to that knowledge in the area of pharmacokinetics that that person would have general pharmacokinetic method and principles understood, that they would know the specific pharmacokinetic parameters of doxycycline, they would know the absorption characteristics of doxycycline, and the resulting blood plasma concentration profiles as well as relied on extensive clinical database that was available on this drug.
Q. Now, we heard from Dr. Rubas regarding many of the specific pharmacokinetic parameters and absorption and so on. Did you rely on the same materials that he relied upon?
A. Yes, I did.
Q. Did you also consider the opinions of Dr. Rubas?
A. I did.
Q. How did the opinions of Dr. Rubas relate to your own opinions?
A. They reinforced my opinions in understanding of the general knowledge required.
Q. With the combination of this background information and the information in the '932 application, what did you conclude?
A. That all of the asserted claims of the Chang patent

are obvious.

Q. Let's talk now about your second obviousness opinion. Does this opinion reflect a combination of references?

A. It does, yes.

Q. And what is that combination?

A. The Ashley '932 application combined with the patent '304.

Q. Please describe the '304 patent generally.

A. Yes. It is a patent issued in April of 1994 and focused on systems and formulations providing a minimum therapeutic blood level of minocycline for at least 24 hours for once daily dose administration.

MR. REED: Your Honor, I offer DTX-2119.

MR. O'MALLEY: No objection.

THE COURT: It is admitted.

(DTX-2119 received into evidence.)

BY MR. REED:

Q. What does the '304 patent teach about how often the minocycline is administered?

A. It teaches that it should be administered once daily.

Q. And what does it teach about the range of blood plasma concentrations achieved?

A. Among other ranges, it talks about a minimum target range of about 0.1 to 1.0 micrograms per mil. And this is found in the '304 application on page 1.

Q. What does the '304 patent say about how to achieve the blood plasma concentrations?
A. I won't go through the actual statement here pulled from the '304 application, but basically it teaches a mixture of IR and DR pellets, where the DR pellets are coated with enteric polymers.
Q. And what does the '304 patent say about a mixture of pellets? What mixture does it teach?
A. Well, it teaches a range of mixtures of IR to DR pellets. That range goes from about 20 to 80. That would be 20 IR, 80 DR to about 80 IR to 20 delayed release.
Q. How is that relevant to the Chang patent?
A. It's quite relevant since it discloses, and for this range, encompasses the range that is expressed more or less as percent of 75 to 25 IR to DR. It also states that this ratio of IR to DR was already generally contemplated and obvious.
Q. What does the '304 patent teach about excipients?
A. It teaches the use of standard pharmaceutical excipients, including those that would permit release in the upper small intestine, particularly the duodenum, and that is shown here spelled out specifically in the '304 application on page 11.
Q. Now the '304 patent is about minocycline; right?
A. Yes.

Q. Why do you feel it was appropriate to combine the '932 application with the '304 patent?

A. Well, first, the Ashley application, '932, discloses minocycline along with doxycycline as a compound that can be used to treat rosacea. And that is found in the '932 application on page 7 as I have shown here.

Minocycline and doxycycline are both very well known second generation tetracycline compounds. They are similar chemically and physically and demonstrates pharmacokinetics that are similar.

And based on all of this, my conclusion and opinion is that substitution of minocycline with doxycycline would be reasonably expected to be successful.

Q. Now, when you do combine these two references, the '932 application and the '304 patent, what do you get?

A. I get, again, reinforcement of the information alone from '932 that one of ordinary skill in the art prior to 2003 would be motivated to combine these two references and that the combination leads to an obviousness of the Chang asserted claims.

Q. And it's your opinion that the '304 patent combined with the '932 application renders all asserted claims of the Chang patent obvious; is that right?

A. Yes.

Q. Let's turn to --

MR. REED: I can't remember if I offered DTX-2119, the '304 patent.

MR. O'MALLEY: I can't either but don't object.

THE COURT: It's admitted, or admitted again.

MR. REED: Thank you.

(DTX-2119 was admitted into evidence.)

BY MR. REED:

Q. Can you please tell us about your third obviousness opinion? Does this reflect a combination of references?

A. Yes.

Q. What combination?

A. Again, the Ashley '932 application and the patent '819 issued in the U.S.

MR. REED: Your Honor, I offer DTX-2116, the '819 patent.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2116 was admitted into evidence.)

BY MR. REED:

Q. Can you please describe the '819 patent?

A. Yes. It's directed towards oral pulsed dose drug delivery technology. It's assigned to Shire Laboratories and it was licensed actually to Galderma. The inventors include Dr. Chang, the inventor of the Chang patent we have been discussing, as well as Dr. Rudnic.

It describes a beadlet technology. These beadlets are in the form of capsules, and essentially it describes the Microtrol technology.

The ratio of immediate release to delayed release can be determined by other means. There's no -- no restriction on that ratio.

More specifically, as we heard from Dr. Rudnic, it does eventually get directed towards controlled release of amphetamines, that these amphetamines are comprised into immediate release and enteric or delayed release components in a capsule.

Q. And I can't recall. What did you say about the date of the '819 patent?

A. It was issued in the year 2001.

Q. Okay. What did you notice about the language in the '819 patent regarding incipient -- excuse me -- excipients?

A. Quite interestingly enough, when you looked at -- when I looked at these two patents and focused on a couple of areas, disintegrants and filling agents, I found remarkable parallelism between these two. In fact, word for word identical phrases and disclosure of specific excipients and their preferred amounts. Likewise, the same thing for filling agents. It's typically as you see in patents like this, a laundry list of various materials, but in this case,

it's identical in both applications, both patents.
Q. To be clear, the two patents that we're talking about here are not your obviousness combination; is that right?
A. No.
Q. This is the '819 patent, which is part of your third obviousness combination, plus the asserted Chang patent?
A. Yes.
Q. And Dr. Chang was one of the inventors on both of these two patents; is that right?
A. Yes.
Q. Why is the language so similar?
A. I would say that it was -- it reenforces the obviousness of certainly this element of the use of excipients and the generation of multi-particulate drug release formulations.
Q. And what does the '819 patent teach about controlled release, generally speaking?
A. It teaches that one can combine immediate release and delayed release components to provide a desired delivery profile.
Q. The Microtrol technology described in the '819 patent, that was one of the off-the-shelf technologies you referred to earlier in your testimony?
A. Yes, it is.
Q. What do you get when you combine the '932 application

with the '819 patent?
A. It reinforces the opinion that Ashley is, when combined with this application, that all of the asserted Chang claims are -- excuse me -- rendered obvious.
Q. Okay. What opinion have you formed about written description?
A. In terms of written description in the Chang patents, it's my opinion that it lacks written support and description for the narrow range of plasma concentrations required by claims 4 and 18.
Q. Now, what do these two claims have in common?
A. They, in the first case, claim 4 is dependent on one and provides for this narrower steady state blood level between 0.3 and 0.8. And then claim 18 is dependent on 15. And, again, recites the same desired steady state -- required steady state plasma levels, between 0.3 and 0.8 micrograms per ml.
Q. And what is the basis of your opinion that the Chang patent lacks written description of claims 4 and 18?
A. Well, I have reviewed the Chang patent in great detail and in no place could I find any description written or otherwise of the fact that the claimed composition actually can lead to the desired or stated plasma ranges of 0.3 to 0.8 micrograms per ml.
Q. Well, what did you find in the Chang patent?

A. Well, I found figure 5, which shows the, among other thing m the steady state plasma concentrations obtained from the 75/25 IR/DR preparation. In other words, the Oracea product. And that while the plasma levels do rise above 0.3 early on following the dose, that in this group of subjects, the 14 different subjects in this case, that all of the plasma concentrations as just expressed by the means fall below 0.3 micrograms per ml, even before 12 hours had elapsed. This would be less than half the required dosing interval.

Q. How low do these levels go in figure 5?

A. They go below 0.2 micrograms per ml.

Q. Let's move now to the last of your opinions. What is the last opinion you formed?

A. This opinion is that there is no evidence that Mylan's proposed generic formulation will infringe on claims 4 and 18 of the Chang patent.

Q. What studies were conducted using Mylan's product to determine the steady state Cmax achieved with Mylan's product?

A. To my knowledge, no such studies have been performed.

Q. So there's simply no data that demonstrates that Mylan's product results in a steady state Cmax of between .3 to .8 micrograms per milliliter; is that right?

A. Yes.

Q. You heard Dr. Rudnic talk about bioequivalency between Mylan's product and Galderma's product and used that to link Mylan's product to the pivotal PK study conducted with Galderma's product; is that right?

A. Yes. Yes.

Q. You understand that Mylan's label refers to that pivotal PK study?

A. I do.

Q. And you understand that Mylan's product refers to that pivotal PK study because the FDA requires it to do so?

A. Yes.

Q. Do you recall how many subjects that study involved?

A. That subject -- excuse me. That study involved 31 subjects.

Q. In that study of 31 subjects, how many of them showed steady state plasma concentrations that stayed between .3 and .8 micrograms per milliliter throughout the 24-hour testing period?

A. Of the 31 subjects, only one.

Q. Do you recall how much higher than .3 that one subject's steady state plasma concentration was at 24 hours?

A. It was what could be described as barely above. It was 0.001 nanograms per milliliter.

Q. Okay. Now, Dr. Rudnic included others by rounding

the values. Do you agree that rounding the values of the other subjects reported in the pivotal PK study is appropriate?

A. In some instances, rounding is appropriate. However, rounding is dependent upon the units employed. In this case, to choose micrograms per ml when all of the values reported from the biostudies are reported in nanograms per ml to more significant digits.

Applying rounding rules in those cases would reflect at best only very small changes and would not allow one to say that someone with a concentration of 0.251 is equivalent to the same as 0.3.

Q. Now, in your experience, would it be appropriate to look at individual data from a study like this pivotal PK study?

A. Typically, one would look at average data and the error associated with whatever PK parameter you are interested in.

Q. Why would it be more appropriate to review average data?

A. One, it's typically scientific standard practice. When you look at most research reports, and if you even look at the Chang patent, all the figures presented are means. There are no individual data there. And, in addition, as, from a regulatory point of view, the FDA requests that they

see the pharmacokinetic data expressed as means and plus the percent coefficient of variation.

Q. If you were to look at the mean data from the pivotal PK study, would it fall within .3 and .8 at all times during the 24-hour period?

A. No.

Q. From your perspective, then, what evidence does Mylan's label, which references this pivotal PK study, provide in terms of evidence regarding infringement of claims 4 and 18 of the Chang patent?

A. I found no evidence that the label provides information that the product will lead to steady state plasma levels of between 0.3 and 0.8 micrograms per ml.

Q. Turning next to Mylan's formulation, can you tell us a little about Mylan's proposed formulation compared to Galderma's formulation and what that means about the Cmax and Cmin?

A. Okay. Mylan's formulation is -- is a capsule based, as is the Oracea product. However, the pellet portion, if you will, differs. Mylan uses a mini tablet formulation wherein the drug is dispersed throughout the powder and then compressed, and then if delayed release is required, as it is, that's coated with an enteric polymer.

The technology of -- used by Shire is based on a sugar with various layers of coating of drug, binders and

other polymeric materials to get the desired dissolution profiles.

THE COURT: Is there an objection?

MR. O'MALLEY: Beyond the scope of expert opinion, your Honor.

THE COURT: It's noted.

BY MR. REED:

Q. I think you said this a few minutes ago. Well, what effect would that have on the Cmax and Cmin?

A. Well, it means that you're not automatically going to get the exact same pharmacokinetic parameters as the Oracea formulation.

Q. I think you said this a few minutes ago, but would you tell us again, how much higher than .3 micrograms per ml the one subject in the pivotal PK study that Dr. Rudnic testified about, how much higher it was at the 24-hour time period?

A. At the 24-hour time period, that one subject of 31, it was one one billionth of a gram.

Q. Would the formulation differences between the Mylan product and Galderma's Oracea product be sufficient to change a patient's Cmin or, excuse me, Cmax by one one billionth of a gram per ml?

MR. O'MALLEY: Same objection, your Honor.

THE COURT: It's noted.

THE WITNESS: Yes.

MR. REED: No further questions.

THE COURT: All right. We will take our morning recess and then we'll have cross-examination.

(Brief recess taken.)

THE COURT: You may proceed.

MR. O'MALLEY: Thank you, your Honor.

May I approach?

THE COURT: You may.

(Binders passed forward.)

CROSS-EXAMINATION

BY MR. O'MALLEY:

Q. Good morning, Dr. Friend.

A. Good morning.

THE WITNESS: Is this a good volume here.

THE COURT: So far so good. Try not to get too close.

THE WITNESS: Okay.

BY MR. O'MALLEY:

Q. Dr. Friend, over the course of your career, you developed new drug formulations; correct?

A. Yes.

Q. You have never had any professional experience with respect to doxycycline; correct?

A. That's true.

Q. And you have never formulated a tetracycline class compound; correct?
A. Correct.
Q. And you had no experience of formulating a drug that is an antibiotic compound formulated at sub-antimicrobial doses; correct?
A. Correct.
Q. Now, you understand that the Chang patent claims controlled release formulations for a once daily doxycycline treatment; correct?
A. Yes.
Q. It's difficult to develop a controlled release drug product that makes it all the way to the market, wouldn't you agree?
A. It can be challenging.
Q. In fact, over the course of your 25 year career, you have never been involved in the formulation of any drug product that is, or has been, marketed; correct?
A. Not directly. Indirectly, some technology of mine has been used in commercial products.
Q. But not directly?
A. Not directly.
Q. In fact, you have been involved in approximately 30 to 40 drug formulations that never made it as far as clinical trials; correct?

A. Yes.
Q. And most of those, in fact, around 95 percent of those, as you estimated them, were controlled release formulations; correct?
A. Correct.
Q. Now, based on your own experience, even when a skilled formulator makes a reasonable prediction that a particular formulation will work, that formulation is unsuccessful about 50 percent of the time when tested in humans; correct?
A. It could be. I'm not sure if it's 50, 60, or 40 percent.
Q. But that is a reasonable ballpark; correct?
A. Reasonable, yes.
Q. Now, let's talk about your infringement opinions first, if we may.

Specifically, you offered infringement opinions as to claims 4 and 18; is that correct?
A. Yes.
Q. I prepared a demonstrative for our help which includes claims 4 and 18 along with their independent claims as PDX-600. If we can put it up there.

And if it's easier for you at any point, Dr. Friend, the Chang patents at PTX-5 in the larger of the two notebooks.

Let me know when you are with me, sir.

A. Yes.

Q. Okay. Now, you understand that claims 4 and 18 only differ from their respective independent claims in that the patient taking the dosage must also have the blood levels in the narrower concentration range of between .3 microgram per milliliter to .8 microgram per milliliter; correct?

A. Yes.

Q. You may need to speak up just a hair.

A. Okay.

Q. And it's your expert opinion that Mylan's generic product would not infringe those narrower concentration ranges; correct?

A. Yes.

Q. Now, in formulating your expert opinion, did you take into account Mylan's assertion to this Court in this case that it's mean trough or Cmin doxycycline serum concentration of its proposed ANDA product is .3 microgram per milliliter?

A. I don't recall such an assertion.

Q. Okay.

A. Statement.

Q. The first tab in your larger of the two notebooks is PTO-Exhibit 3. Do you see that?

A. Yes.

Q. Would you turn to paragraph 39 of PTO-Exhibit 3, page 11.

A. Oh, I'm sorry.

Q. Let me know when you have that, sir. It's also on your screen if at any time any of these references become easier --

A. Okay.

Q. -- to fiddle around with rather than a notebook.

A. Yes, I see that.

Q. Are you with me?

A. Yes.

Q. You probably are not familiar with this document, I take it?

A. It doesn't appear to be one I have seen before. No.

Q. So, naturally, you didn't employ this document in your opinions of noninfringement?

A. No, I did not.

Q. Well, I will represent to you this is the so-called Mylan's statement of contested facts, a portion thereof that was submitted to the Court prior to the trial in this case.

Turning to paragraph 39, do you see where it says that the mean trough doxycycline serum concentration of Mylan's proposed ANDA product is .3 micrograms per milliliter?

A. Yes, I see that.

Q. And mean trough is another way of saying mean Cmax; correct?

A. Mean Cmin.

Q. Oh, I'm sorry. It's another way of saying mean Cmin; correct?

A. Yes.

Q. And a mean Cmin of .3 would be within the ranges of claims 8 and 14; correct?

A. It would be.

Q. Now, if we take paragraph 38 of Mylan's statement of contested facts, naturally, you didn't take this paragraph into account in your opinions; is that correct?

A. That's correct.

Q. And you see where they report a mean Cmax for the single dose 40 milligram capsule -- Mylan capsule at steady state?

A. Yes.

Q. And you see they report a figure of .6 for that?

A. Yes.

Q. And that, again, would be within the concentration ranges of claims 8 and 14; is that correct?

A. Yes. At the time of Cmax, yes.

Q. Now, I'd like to turn now to your invalidity opinions, if we may. Now, today you testified as to invalidity of the Chang claims based on several prior art

references; correct?

A. Yes.

Q. Now, most or all of those references were provided to you in the first instance by Mylan's counsel; is that correct?

A. That's true, yes.

Q. Now, were you in the courtroom earlier when Dr. Rubas began to talk about something called an absorption window?

A. I was.

Q. And you are familiar with the term "absorption window;" correct?

A. I am.

Q. An absorption window is an area in the gastrointestinal tract in which a drug is well absorbed or absorbed at a sufficient rate as compared to other regions where the drug is absorbed more slowly or not at all; correct?

A. Yes.

Q. Now, the establishment or prediction of an absorption window for a particular drug needs to be confirmed by clinical testing; correct?

A. Proof of an absorption window, yes.

Q. An absorption window is something that a person of ordinary skill in the art should consider when designing or formulating a drug; correct?

A. Correct.
Q. Indeed, under certain circumstances, the existence of an absorption window makes developing a controlled release formulation more challenging relative to a drug without absorption window; isn't that true?
A. Yes, if challenging means you would need to perform more experiments and spend more time in the development process.
Q. Now, today it's known that doxycycline has an absorption window; correct?
A. The data support that conclusion, yes.
Q. Now, in your direct testimony, I did not hear you present opinion that it was known prior to 2002 that doxycycline has an absorption window. Did I miss that or am I correct?
A. No, I did not express an opinion.
Q. Now, in forming your opinions in this case, you did not even consider what a person of ordinary skill in the art would have thought had the doxycycline absorption window not been known in 2002; correct?
A. Correct. Excuse me.
Q. In your own experience, you have worked with drugs that have an absorption window; correct?
A. Correct.
Q. In fact, you worked on an attempted formulation of

the drug rantinidine (phonetic) and I might have mispronounced that.

A. Close. Ranitidine.

Q. Ranitidine. That has an absorption window; correct?

A. Correct.

Q. And you were unable to develop a successful controlled release formulation of that particular drug; correct?

A. Correct.

Q. And am I also correct that that is the only drug that you attempted to develop a controlled release formulation that had this absorption window?

A. Correct.

Q. Now, in your opening or direct testimony, rather, today, you relied on the Ashley references, the '304 patent and the '819 patent; correct?

A. Correct.

Q. Now, in your expert report, however, you previously relied on a number of -- I count seven other references to support your opinions of invalidity; correct?

A. That is correct.

MR. O'MALLEY: And if we could just put up on the screen -- we're just going to ask a quick question so the screen may be sufficient. Would you put up DTX-2117, please.

This is one of the references that you relied on in your expert report to support your opinions of invalidity of the Chang patents; correct?

A. Correct.

Q. And today you provided no testimony with respect to that reference; is that correct?

A. Yes.

MR. O'MALLEY: Would you put up, please, DTX-2120.

BY MR. O'MALLEY:

Q. And this reference, which I will call the Walker reference, is a reference that you relied on in your expert report to support your invalidity opinion; correct?

A. Correct.

Q. And today you provided no testimony as to that reference; is that correct?

A. That's correct.

Q. And with respect to Thomas 2000, DTX-2121, same question, you relied on in your expert report; correct?

A. Correct.

Q. No testimony today?

A. No testimony, no.

MR. O'MALLEY: Okay. PTX-206, please.

BY MR. O'MALLEY:

Q. It is a little hard to read, but do you recognize

this to be the Periostat tablet label?
A. I do, yes.
Q. And you relied on this to support your invalidity opinions in your expert report; correct?
A. Correct.
Q. And no testimony today; correct?
A. Correct.
MR. O'MALLEY: And DTX-2118, please.
BY MR. O'MALLEY:
Q. Similarly, you relied on this in your expert report to support your invalidity; correct?
A. Correct.
Q. And no testimony today?
A. That's correct.
MR. O'MALLEY: I think are almost at the end. DTX-2123, please, which I will call the Ashley presentation.
BY MR. O'MALLEY:
Q. You relied on it in your expert report to support your invalidity opinions; correct?
A. Yes.
Q. And no testimony today?
A. No, no testimony.
Q. Now, let's talk about your testimony with respect to the Ashley rosacea references; okay?
A. Okay.

Q. And you know what I'm referring to by the Ashley rosacea references?
A. You are referring to '932 and the related applications?
Q. That's correct.
A. Not the '854.
Q. No, the '854 we can call the Ashley controlled release references. Is that fair for our communication?
A. Okay.
Q. So if I refer to either the '932 or the Ashley rosacea references, you will understand I'm referring to the same thing?
A. Yes.
Q. Okay. Now, it's at DTX-2111 in your notebook if you need it. I'll wait until you have it in front of you.
A. Okay.
Q. Now, the '932 patent application does not explicitly disclose the use of a 30 milligram IR component; correct?
A. Correct.
Q. And the '932 patent application does not explicitly disclose the use of a 10 milligram DR component; correct?
A. Correct.
Q. And the '932 application does not explicitly disclose the ratio of 30 milligrams to 10 milligrams IR to DR; isn't that correct?

A. Yes, not explicitly. It does not.
Q. And do you recall -- well, let me ask you this. Were you in the courtroom, I guess it was Tuesday, Dr. Friend, when the opening statements were made?
A. Yes, I was here.
Q. And do you recall that in the opening statement of Mylan's counsel, he referred to this 30 to 10 IR/DR ratio as the so-called secret sauce of the Chang invention?
A. Something along those lines, yes.
Q. And do you recall that Mylan's counsel conceded in his opening statement that the Ashley patents do not disclose this 3 to 1 ratio, the so-called secret sauce?
A. Yes.
Q. And you don't dispute that?
A. I do not.
Q. Do you understand that for anticipation, each and every limitation of the patent claims must be found in a single reference?
A. I do.
Q. But, again, the 30 to 10 ratio is not disclosed in the Ashley patents; correct?
A. Not explicitly.
Q. Okay. Now, you also testified as to some disclosures from the Ashley rosacea references; correct?
A. Yes.

Q. And for your slides, you used the '854 but for purposes of your opinions, you have testified previously there is no distinction between that reference and another reference in the same family such as the '106 application; is that fair?

A. That is what I said at deposition, yes.

Q. Do you agree with that?

A. Yes.

Q. Okay. Now, before I move to the rosacea references, returning back briefly to the -- well, no. Let me stay with the Ashley rosacea references. None of those slides that you discussed the rosacea references talked about a single complete embodiment of a controlled release formulation from those references; correct?

A. For the '932? Yes. There was no complete formulation, if you will. I understand you correctly.

Q. There is no embodiment or example of a complete formulation anywhere in the '932; correct?

A. Correct.

Q. So, naturally, there is no disclosure of a complete formulation that will give steady state blood levels of doxycycline of a minimum of .1 micrograms per milliliter and a maximum of 1.0 microgram per milliliter?

A. If you take the '932 in isolation, yes, that's correct.

Q. And there is no expressed disclosure of any single complete formulation that included both an IR and a DR portion in the '932; correct?

A. Correct.

Q. And there is no expressed disclosure of any specific embodiment or example of a formulation that had an IR portion with a 30 milligram doxycycline; correct?

A. Correct.

Q. Or a DR portion with a 10 milligram doxycycline; correct?

A. That's correct.

Q. And there is no specific complete example or embodiment of any formulation in the '932 with a DR portion in the form of pellets coated with at least one enteric polymer; correct?

A. Correct.

Q. And it's your opinion that the Ashley references are the closest prior art; is that correct?

A. Yes. As I said earlier, though, the combination of those two references, '854 and '932.

Q. All right. But let's talk about then the Ashley CR references. And I got a little bit ahead of myself before, but, again, there's no difference between the '854 you discussed versus the one of the other in that family. For example, the 106; correct?

A. Correct.
Q. Now, you presented some slides today on the Ashley controlled release references; correct?
A. Correct.
Q. And you testified as to the portions of the disclosure from the Ashley CR references that you rely on for your invalidity opinion; is that correct?
A. Correct.
Q. And none of those slides that you presented to the Court today with respect to the Ashley CR patents, again, disclose the single complete example or embodiment of CR formulation; correct?
A. Correct.
Q. Because in the Ashley CR references, just like the Ashley rosacea references, there is no disclosure of a single, complete example or embodiment of a controlled release formulation; correct?
A. Correct.
Q. And there's no explicit disclosure, I think you've answered this already with respect to the secret sauce, of any particular ratio of IR to DR, doxycycline, in the Ashley CR references; correct?
A. No, no specific ratio is presented.
Q. Now, given the fact that there's no example or embodiment of a single complete formulation in the Ashley CR

references, and naturally there's no disclosure of such a formulation that will give steady state blood levels of a minimum of between .1 microgram per milliliter and a maximum of 1.0 microgram per milliliter; is that correct?

A. Correct.

Q. And there's no express disclosure of an example or embodiment of a complete formulation that includes both an IR portion and a DR portion; is that correct?

A. No explicit statement, no.

Q. And there's no express disclosure of a complete example or embodiment of a particular formulation with an IR portion of about 30 milligrams doxycycline; is that correct?

A. Correct.

Q. And there's no express disclosure of such a formulation with a DR portion of ten milligrams; correct?

A. Correct.

Q. And no express disclosure much such a formulation with the ratio of 30 to 10 IR to DR; is that correct?

A. That's true, yes.

Q. And no express disclosure of any such specific formulation with a DR portion in the form of pellets coated with at least one enteric polymer; correct?

A. Not explicitly, no.

Q. Okay. Now, let's look at your slide, if we may,

DDX-623.

Now, if I recall correctly from your testimony, you rely on this disclosure from the Ashley CR references to support your opinion that the ratio of IR to DR in the Chang claims is anticipated; is that correct?

A. Yes. In part.

Q. In part. And further in part by relying on Rubas' testimony; is that correct?

A. Correct.

Q. And naturally Rubas' testimony is not incorporated explicitly in the Ashley disclosure; is that correct?

A. Correct.

Q. Now, the Ashley CR references can disclose many combinations of immediate and sustained and delayed release phases; correct?

A. Correct.

Q. In fact, let's take a look at your DDX-621. And as you pointed out, the composition also can include a controlled release agent selected from the group consisting of an instantaneous release agent, and you pointed out delayed release agent and combinations thereof.

It can also include the portion you didn't highlight of sustained release agent; is that correct?

A. It could.

Q. Okay. And if we can turn to DTX-1067, page 10. And

let's focus on the bottom paragraph, please.

And this is from the 106 application. And it states, "In a preferred embodiment, the composition of the invention comprises more than one controlled release agent, and can include all three types of controlled release agents, i.e., an instantaneous release agent, a sustained release agent, and a delayed release agent."

Do you see that?

A. I do.

Q. And so according to the disclosure of the Ashley CR references, the Ashley patent teaches that you can have for its controlled release composition a combination of instant release and sustained release; is that correct?

A. Yes.

Q. You can have a combination of instant release and delayed release; correct?

A. Correct.

Q. You could have sustained release by itself; is that correct?

A. Yes.

Q. You could have delayed release by itself; is that correct?

A. Correct.

Q. Or you could have all three: Immediate release, delayed release, and sustained release; correct?

A. Correct.
Q. Now, going back to your slide 623, DDX-623. Now, you focused on the highlighted language, and I will read it again into the record. "It is preferred that at least 50 percent, more preferably greater than 80 percent of the tetracycline in the composition be released in the upper G.I. tract."
Correct? You've focused on that?
A. Yes.
Q. And you testified that that is a relatively narrow range of ratios. Did I hear you correctly?
A. It suggests a narrow range of ratios, yes.
Q. Now, for the purposes of trying to pick out a piece of disclosure that would anticipate the Chang claim, you have to get rid of that disclosure of greater than 80 percent being immediately released; is that correct?
A. Well, I interpreted the claim of -- in one of about 30 and about ten to mean ranges possibly -- not specifically those numbers, but ranging outside because of the about language.
Q. Now, it states that more preferably greater than 80 percent will be released in the upper G.I. tract; is that correct?
A. Correct.
Q. Now, if you just take the preferred language of at

least 80 percent, and given the combinations that we already said are within the disclosure of the Ashley CR, namely, IR/SR, IR/DR, SR by itself, IR/DR/SR, in those teachings, it would suggest a myriad of compositions, wouldn't it?

A. It could, yes.

Q. In fact, the disclosure of the Ashley CR reference could be met by a single phase SR gastro-retentive form; correct?

A. Potentially.

Q. In fact, the reference in the portion of the disclosure you cite to refers to the fact that the formulation is entrapped in the upper portion of the gastrointestinal tract.

Do you see that?

A. I see that, yes.

Q. And that means a dosage form that's retained in the stomach due to its size; correct?

A. That's my interpretation, yes.

Q. So that could be, for example, a gastro, so-called gastro-retentive formulation that released 80 percent over a longer period of time; is that correct?

A. Longer period of time than what?

Q. Over a longer period of time relative to immediate release.

A. Yes.

Q. Okay. And a gastro-retentive formulation is different from an immediate release formulation; is that correct?
A. It depends.
Q. Well, for example, an immediate release dosage form is not generally retained in the stomach due to its size; correct?
A. That's true, yes.
Q. And that is by contrast a characteristic of a gastro-retentive formulation; correct?
A. Correct.
Q. Now, there's nothing in the portion of the disclosure you rely on that states that there should be a delayed release component; correct?
A. Just kind of repeat that question.
Q. Yes. There's nothing in the paragraph you rely on for the anticipation of the IR/DR ratio that states that there should be a delayed release component at all; is that correct?
A. It doesn't explicitly state the need for a DR portion, correct.
Q. Okay. Now, let's return to the portion that we looked at DTX-1067 at the bottom of page 10. And, again, there's discussion of an embodiment of the Ashley CR reference that includes all three types of the controlled

release agents; correct? IR, SR and DR; is that correct?

A. That's correct.

Q. And they state that using all three types of those controlled release agents can produce a profile that administers the tetracycline compound in a specific dose over an extended period of time, for example, 12 to 24 hours. And then they refer to figure 1 that depicts that release profile.

Do you see that?

A. Yes.

Q. Now, figure 1 was also part of your slides; correct? DDX-607, if I'm not mistaken?

A. That's correct.

Q. Now, again, no specific example of a complete formulation is provided in the Ashley CR references that would create the release profile of figure 1; is that correct?

A. Yes, correct.

Q. And you see, according to the disclosure, that reference figure 1, it has incorporated three different release phases, an instantaneous release, a sustained release, and a delayed release.

Do you see that?

A. Yes, I do.

Q. And apparently, according to the disclosure, that's

to give continuous release over a period of 12 to 24 hours; is that correct?

A. Yes.

Q. Now, the 30-milligram IR to ten-milligram DR formulation that Chang claims would create a very different release profile than shown in figure 1; correct?

A. Well, like I said earlier in my testimony, these -- this figure presents blood plasma levels which aren't necessarily reflective of release profiles.

Q. Well, I believe you also showed us a release profile for the Ashley 30 IR 10 DR milligram formulation, as I recall, DDX-602, perhaps.

A. Yes, I did.

Q. Okay. Let's -- I have the wrong number. Let me pull up PDX-602, which is a demonstrative we created.

Do you recognize on the left is another form of figure 1 from one of the other Ashley CR patents?

A. Yes.

Q. And that one is from the 106. And then on the right, is another representation of the figure that you testified about in your written description portion of your testimony; is that correct?

A. Yes.

Q. And that is a plasma concentration graph for the claims of the Chang patent, 30 IR, 10 DR; is that correct?

A. Correct.
Q. And you can see that it provides for a very different plasma concentration profile relative to the only plasma concentration profile provided by the Ashley CR references; is that correct?
A. They're not identical, no.
Q. They're different. They're rather different, wouldn't you agree, Dr. Friend?
A. They're different, yes.
Q. Okay. So if you were trying to follow the disclosure of Ashley with respect to the only release profile it disclosed, you would not be successful if you tried a 30-milligram IR to 10-milligram DR combination; is that correct?
A. Yes. Yes.
Q. Now, I would like to move on, Dr. Friend, to talk about the '304 reference that you testified about.
A. Okay.
Q. And if you need to refer to it, circumstances it's at DTX-2019.
A. Okay.
Q. And as I believe you testified, the '304 patent discloses a controlled release formulation of minocycline; is that correct?
A. Correct.

Q. And minocycline and doxycycline have different physical and chemical properties; correct?

A. "Different" needs to be defined within a range of possible differences.

Q. Well, did you testify in your deposition that the two drugs have different chemical and physical properties?

A. They're -- they're different, but similar.

MR. O'MALLEY: Would you give me transcript page 143, 9 to 17.

And the transcript, Dr. Friend and your Honor, is provided in the thinner of the two notebooks I've handed up. I think it's the first tab.

MR. REED: What page?

MR. O'MALLEY: Page 143, Line 9 to 17. It's on the screen.

"Question: And minocycline and doxycycline have different physical and chemical properties; correct?

"Answer: That's a relative term. They are relatively similar in the big scheme of pharmaceutical products.

"Question: Okay. But do they have different physical and chemical properties; correct?

"Answer: Yes."

MR. REED: Your Honor, this is not impeaching.

THE COURT: That's an objection. It's

overruled.

Go ahead.

BY MR. O'MALLEY:

Q. We asked you those questions and you provided those answers; correct?

A. I did.

Q. All right. Now, turning to the '304 patent, you don't consider the '304 patents to be as close to the Chang patent claims as the Ashley references; correct?

A. Correct.

Q. And the '304 patent, again, was brought to your attention by Mylan's counsel; is that correct?

A. Correct.

Q. And the '304 patent does not disclose a once-daily formulation of doxycycline; is that correct?

A. Correct.

Q. And the '304 patent does not disclose the 75 to 25 IR/DR ratio of doxycycline of the Chang claim; is that correct?

A. Not of doxycycline, no.

Q. It does not disclose the so-called secret sauce; correct?

A. Not for doxycycline.

Q. Well, you said not of doxycycline. For the disclosure you rely on for the concentration I believe that

is on DDX-652.

MR. O'MALLEY: Can we pull that up?

BY MR. O'MALLEY:

Q. Am I correct that's the disclosure?

A. Yes.

Q. All right. So the IR portion can be anywhere from 20 to 80 percent; correct?

A. Correct.

Q. And the DR portion could be conversely anywhere from 80 to 20 percent; correct?

A. Correct.

Q. That's a huge range of possible combinations of IR and DR; correct?

A. Correct.

Q. The '304 patent does not disclose methods of treating rosacea; correct?

A. Correct.

Q. Now, you discussed some of the blood plasma concentrations levels that were disclosed by the '304 patent. Do you remember that?

A. In the '304 patent? Can you refresh my memory.

Q. Well, let me just ask the question differently so I don't have to find you a slide.

The Cmax of the formulations described in the examples of the '304 patent are much higher than the 1.0

microgram milliliter limit of the Chang claims; correct?
A. Yes, there is a range of potential concentration ranges that are disclosed in the '304 application.
Q. They're much higher than the Chang upper limit; correct?
A. Most of these examples are, yes.
Q. In fact, all of them are; correct?
A. The lower range disclosed a 0.1 to 1.0 micrograms per mil minocycline.
Q. Micrograms per mil or a different MCG per mil?
A. Micrograms.
Q. Now, do you recall, when you were asked in your deposition, "do you understand that the Cmax of the formulations described in the examples of the '304 patent have Cmax that are much higher than 1.0 micrograms per milliliter?" Do you recall?
A. Yes.
Q. And do you recall answering "I do?"
A. I do recall answering "I do."
Q. And as you testified today, the point of the '304 patent is to keep blood plasma levels of minocycline above the therapeutic minimum; correct?
A. Yes.
Q. And the point of it is to keep the blood plasma levels in the concentration range where they would act as an

antibiotic; correct?

A. Yes. From that range, high range to a minimum. Right.

Q. And you understand that by contrast, the point of the Chang blood plasma concentration upper range limitation is to keep blood plasma concentration below that which would allow the doxy to act as an antibiotic; correct?

A. Correct.

Q. Now, if we go back to DDX-3650.

And if you look at the bottom box, does that refresh your recollection that the units are not micrograms per milliliter in the '304 patent?

A. MC I think is an abbreviation for micro.

Q. Okay. You believe that is the same?

A. Yes.

Q. Now, you are not aware of any disclosure in the '304 patent of anything other than an antibiotic dose of minocycline?

A. That's correct.

Q. And you are not aware of any once daily minocycline product that is formulated according to this patent or disclosed in this patent using IR and DR multiparticulate pellets; correct?

A. Correct.

Q. Now, you also relied on the '819 patent for your

invalidity opinions; correct?

A. Correct.

Q. And if you need it, that's at DTX-2116 in your book, sir.

A. Okay.

Q. All right?

A. Thank you.

Q. Now, you were in the courtroom Tuesday when Dr. Rudnic testified as to his personal involvement with the development of the inventions claimed in the '819 and other related patents; correct?

A. Correct.

Q. And you heard that the products covered by the '819 patent are among the 80 products that reached the market for which Dr. Rudnic was involved in the formulation; correct?

A. Yes.

Q. And again, by contrast, you were not personally involved in the development of the formulations covered by the '819 patent; correct?

A. Correct.

Q. And you were not personally involved in fact in the formulation of any drug that has been marketed; correct?

A. Correct.

Q. But you disagree with Dr. Rudnic's opinion that this amphetamine patent is very distant from the Chang patent;

right?
A. The use of amphetamines is, yes.
Q. I'm sorry?
A. The use of amphetamines is very far from the Chang patent.
Q. Right. In fact, there is no particular reason why a person of ordinary skill in the art would look to formulations of amphetamines, per se, when trying to formulate a once daily doxycycline formulation; correct?
A. Correct. I could have chosen dozens of other examples. I just choose this one.
Q. The amphetamine example?
A. Yes.
Q. And doxycycline and amphetamines naturally have very different physical and chemical properties; correct?
A. They can, yes.
Q. Now, again, if you can turn to DTX-2117, please. I'm sorry. Let's set that aside for the moment.
Returning to the '819 patent. One of the purposes of the invention of the '819 patent was to provide continuing increasing blood levels of amphetamines over an extended period of time as compared to an immediate release formulation; correct?
A. Correct.
Q. And, again, by contrast, the formulation claimed in

the Chang patent is intended to keep blood plasma levels below a certain ceiling; correct?

A. Correct.

Q. And a formulation such as that disclosed in the '819 patent that provides for continuing increasing blood plasma concentrations could, if employed with doxycycline, exceed the upper concentration limit required by Chang; correct?

A. If one directly applied what is disclosed, yes.

Q. Now, the '819 patent does not disclose 75 to 25 IR/DR ratio of doxycycline; correct?

A. Correct.

Q. It doesn't disclose the so-called secret sauce; right?

A. Yes.

Q. And the '819 patent does not disclose a once daily formulation of any drug that gives a steady state blood level of a minimum of .1 and a maximum of 1.0 micrograms per milliliter; correct?

A. Correct.

Q. And the '819 patent does not disclose the once daily formulation of any drug that gives steady state blood levels of between .3 to .8 micrograms per milliliter; correct?

A. Correct.

Q. And the '819 patent does not disclose any methods of treating rosacea; correct?

A. That's true.
Q. Now, I'll ask you if you would to turn to DTX-2117, please.
Now, again, you are familiar with this reference. As you testified earlier, this is one of the references that you relied on in your expert report but not in your testimony today; correct?
A. Correct.
Q. Now, in your expert report, you took the position that you believe the Chang formulation was virtually identical to the Shire technology disclosed not only in the '819 patent that we just discussed but also the '768 patent; correct?
A. I don't recall exactly.
Q. Okay. You have your expert report in the thinner of your two references. And if we could pull up Friend Opening Report, paragraph 62.
Sir, this is the paragraph where you take the position that Shire's prior controlled release references similarly disclose the use of virtually the identical technology employed by the Chang patent, and you reference, by example, the '819 patent; correct?
A. Yes.
Q. And then in the following paragraph, you say, similarly, you cite the '768 patent for the same purpose;

correct?

A. Correct.

Q. So -- and you understand that both the '819 and the '768 patent relate to what you testified as the Adderall technology or formulation?

A. Yes.

Q. And I believe you said they both employ the so-called Microtol technology. Did I get that correct?

A. Microtrol.

Q. Microtrol?

A. I think that is correct.

Q. And I think you referred to this Microtrol technology as an example of so-called off-the-shelf technologies; is that correct?

A. I did, yes.

Q. Now, just because a technology is so-called off-the-shelf technology, that doesn't mean it's appropriate for formulating all drugs; correct?

A. That's correct.

Q. And just because a person uses a certain so-called off-the-shelf technology for one formulation, that doesn't mean they can't get a valid patent using that same off-the-shelf technology on a later formulation; isn't that true?

A. That's -- I can't answer that. It's too broad a

question.

Q. You can't answer that.

Now, the disclosure of the '768 and the '819 patents are certainly closer to one another than they are to the Chang patent; correct?

A. Yes.

Q. Both the '819 and the '768 patents disclose controlled release formulations of amphetamines; correct?

A. Yes.

Q. Both relate to Shire's technology as applied to the Adderall drug franchise; correct?

A. Correct.

Q. And both patents disclose that the formulations can be combinations of IR and DR multiparticulate drug components; correct?

A. Correct.

Q. And both are intended to deliver in a once daily dosage a therapeutically effective amount of amphetamines to treat attention deficit hyperactivity disorder; correct?

A. Correct.

Q. Now, you testified the '819 and the '768 patent disclosures are closer to one another than they are to the Chang patent; correct?

A. Correct.

Q. And are you aware that the PTO decided that the '768

invention was patentably distinct from this '819 invention that is, by your own testimony, closer than Chang?

A. I'm not aware of that, no.

MR. O'MALLEY: Could we pull up the '768 patent and notice of references? I believe we have a snapshot, gentlemen.

BY MR. O'MALLEY:

Q. Again, you can refer to the portion of the '768, DTX-2117, that is in your notebook. But do you see on the second page of cited references that the '819 patent is disclosed as having been a cited reference in the '768?

A. Yes, I see that.

Q. Do you understand that that indicates that the Patent Office considered the disclosure of the '819 and decided that the '768 was nevertheless patentable?

A. Yes, I understand that.

Q. And, again, they're closer to one another than either are to Chang; correct?

A. Yes.

Q. Now, let's return to your claim chart, which is I think DDX-615.

Now, again, since neither Ashley references you testified discloses any single complete formulation, as you pull citations, you can't pull from a single formulation, naturally, in this chart; correct?

A. No, there is not a specific formulation mentioned in this chart. Correct.

Q. So to meet the various anticipatory opinions with respect to each and every limitation of Chang claim 1, you have to piece together disclosures from various portions of the two references; correct?

A. Correct.

Q. And, again, even if you were to piece together these various separate disclosures from the two references, never will you find an expressed disclosure between the two of them of the 75 and 25 ratio, the so-called secret sauce; correct?

A. No, it's not explicitly stated as such were found.

Q. Now, during your direct testimony, you didn't provide any testimony as to the Faulding company's attempt to formulate doxycycline; correct?

A. Correct.

Q. And you heard Dr. Rudnic talk about the Faulding's company's failure?

A. Yes, I did.

Q. But today you provided no testimony in rebuttal to that; fair enough?

A. Fair.

MR. O'MALLEY: I have no further questions.

THE COURT: Any redirect?

MR. REED: Yes. Thank you, your Honor.

REDIRECT EXAMINATION

BY MR. REED:

Q. Dr. Friend, Mr. O'Malley asked you to look at Exhibit 3 of the pretrial order, the first document in the big binder.

A. Yes.

Q. I'm going to ask you to look back at that as well, please.

A. Okay.

Q. He took us to a paragraph near the beginning of the document. I'd like to take you to a paragraph that appears later in the same document that appears at page 30.

A. Okay.

Q. At the bottom of page 30, there is a numbered paragraph 138. Do you see that paragraph?

A. I do.

Q. Could you read that paragraph, please?

A. It says the mean Cmin of the CR 101 PK study relied on by DJ defendants is 164 nanograms per milliliter plus or minus 70.7 nanograms per milliliter.

Q. Is that consistent with your understanding of the Cmin for the pivotal PK study discussed by Dr. Rudnic?

A. Yes.

Q. Is that also consistent with your opinion that the

Mylan product Cmin will not stay between .3 and .8 micrograms per milliliter?

A. Yes, it is consistent.

Q. Looking at the next page, paragraph number 139, could you read that as well, please?

A. Taking the Cmin standard deviation a range of variability calculated from the population into account, for instance, an upper value of 234.7 nanograms per milliliter or 23 micrograms per milliliter, the upper range of the expected Cmin value is still much less than the 0.3 micrograms per mil plasma concentration required by the claim.

Q. Again, is that consistent with your opinions?

A. Yes, it is.

Q. Do you understand that be to the Cmin that was referred to in the previous paragraph determined by the pivotal PK study that Dr. Rudnic identified?

A. Yes. That's what I understand.

Q. Let's go back to the page that you were asked to look at by Mr. O'Malley. That was page 11 of the document.

A. Okay.

Q. At the end of that paragraph, you see two exhibit numbers referenced.

A. I do.

MR. REED: Your Honor, I would like to

provide copies of that. I have only three, so with the Court's permission, I suggest I give one to the witness, one to opposing counsel and one to yourself.

THE COURT: And these are the two DTX's referenced in paragraph 3?

MR. REED: Yes.

THE COURT: That's fine.

(Mr. Reed handed exhibits to the witness, the Court and opposing counsel.)

BY MR. REED:

Q. Let's take them one at a time. DTX-2274 first.

Do you recognize that document?

A. It's the one I have in my hand, yes.

Q. Do you recognize it?

A. Yes. It's the proposed labeling for Mylan generic equivalent.

Q. And is this the label that you were discussing in your testimony earlier when you said that there's no evidence on Mylan's label of infringement of claims 4 and 18 of the Chang patent?

A. Yes. And I did that by reading a version with larger print than this.

Q. Anywhere on DTX-2274 does it say that the mean trough doxycycline serum concentration of Mylan's proposed ANDA product is .3 micrograms per milliliter?

MR. O'MALLEY: Objection, your Honor. I don't know how he's supposed to answer this. You can't read this exhibit.

THE COURT: We'll see if he can answer it.

THE WITNESS: Yes. In reading this previously, and if I put on my reading glasses, I would be able to find that it's not disclosed anywhere.

MR. REED: Your Honor, I offer DTX-2274.

MR. O'MALLEY: No objection.

THE COURT: It's admitted.

(DTX-2274 was admitted into evidence.)

MR. REED: Let's turn now to DTX-2275, please.

BY MR. REED:

Q. Do you recognize this document?

A. Yes, I do.

Q. And is it a different version of Mylan's label?

A. Yes, it is.

Q. Does it provide a comparison between Mylan's proposed label and the Oracea label?

A. Yes, it does.

Q. Is that what the various columns indicate?

A. Yes. Oracea on the left, Mylan's proposed label in the middle, with some proposed changes on the right.

Q. And does this document anywhere indicate that the mean trough doxycycline serum concentration of Mylan's

proposed ANDA product is .3 micrograms per milliliter?

A. No, it's not disclosed.

MR. REED: I offer DTX-2275, your Honor.

MR. O'MALLEY: No objection.

THE COURT: All right.

(DTX-2275 was admitted into evidence.)

BY MR. REED:

Q. Let's talk for just a minute now about the absorption of doxycycline.

MR. REED: And can we please put up on the screen DDX-506.

BY MR. REED:

Q. What do you know about the absorption of doxycycline prior to April 2003?

MR. O'MALLEY: Objection. Beyond the scope of the direct. His direct or my cross.

THE COURT: I'm sorry. Where is this slide from, Mr. Reed?

MR. REED: This was a slide that Dr. Rubas testified about, and Dr. Friend on his direct testified knowing about the absorption, and then Mr. O'Malley questioned him for several minutes on the absorption window of doxycycline.

MR. O'MALLEY: Not with respect to this exhibit that he did not testify about, your Honor.

THE COURT: Well understood. Dr. Friend will incorporate Dr. Rubas opinion into his, so I'm going to overrule the objection to that question.

BY MR. REED:

Q. Is the Exhibit DTX-2206, which is an article by Saivin, a document you considered in forming your opinions?

A. Yes, it is.

Q. Is it, in fact, a document that you were examined on at your deposition extensively?

A. Yes, I was.

Q. Can you tell us what you know about doxycycline absorption from this reference?

A. From this reference, it states that the absorption primarily occurs in the duodenum. And this also discloses the reason as to why that occurs and that the drug has the greatest liposolubility. Doxycycline is not particularly lipophilic, but it is most lipophilic at pH 5.5 and maximally absorbed at that pH.

Q. Is that consistent with the disclosure in the '932 application about release of a large portion of doxycycline in the upper G.I. tract?

MR. O'MALLEY: 'Objection, your Honor. I hate to launch the first leading objection, but feel compelled to.

THE COURT: Okay. Overruled.

You may answer.

THE WITNESS: Sorry.

BY MR. REED:

Q. Is the information here in DTX-2206 consistent?

A. Yes, it is. Yes, it's very consistent.

Q. Mr. O'Malley asked you a question about a drug that I'm not sure I can pronounce either. Ranitidine?

A. Yes.

Q. What can you tell us about the half life of Ranitidine?

A. Ranitidine has a relatively short half life of between two and three hours.

Q. How is that different from doxycycline?

A. Well, as we heard, the half life is substantially longer. Depending on which reference you look at and so on, it's 17, 18, 19, 20 hours.

Q. For doxycycline?

A. Doxycycline, yes.

Q. How does the difference in half lives matter for purposes of formulating a drug?

A. Well, in the case of doxycycline, it means that there is some latitude in terms of interval of dosings. It's natural that the drug is going to be present in the plasma for very long periods of time following a single dose. In the case of Ranitidine, it's cleared very quickly. And so

the requirements to create a once-daily version of Ranitidine and doxycycline are very much different.

Q. Mr. O'Malley also asked you several questions about prior art references that you had included in your expert report and that you discussed at your deposition, but that you did not present here today.

Do you recall that?

A. Yes.

Q. Do you still believe that those prior art references all anticipate and/or render obvious each of the asserted claims of the Chang patent?

A. I do.

Q. And is there a reason why you did not discuss each and every one of them in light of today?

A. Well, after reviewing the documents as a whole, my opinions were supported by the narrower number, the more limited number of references that were really required to form my opinion. They bolster my opinion, but not required to do what I testified to today.

Q. Is it your understanding we're on a clock for this trial?

A. Yes. Yes. And that was also another reason there really wasn't a practical -- it wasn't a practical consideration of the ability of time to run through all those references.

MR. REED: Your Honor, Mr. O'Malley discussed with Dr. Friend exhibits DTX-1067, also 2117, also 2118, also 2120, also 2123, and 2124, and I offer all of those exhibits.

MR. O'MALLEY: Your Honor, I used those only for impeachment, so not for any evidentiary purpose. So I will object.

THE COURT: The objection is overruled. They're admitted.

(DTX-1067, 2117, 2118, 2120, 2123 and 2124 were admitted into evidence.)

MR. REED: No further questions.

THE COURT: Thank you, Doctor. You may step down.

THE WITNESS: Thank you.

(Witness excused.)

MS. GILL: Your Honor, Kirin Gill for Mylan.

THE COURT: All right.

MS. GILL: Mylan would like to call Robert Ashley by deposition. Mr. Ashley was a named inventor of the '932 and the '854 applications that Dr. Friend testified about this morning.

And before we get to that, we'd also like to move for the admission of a couple of exhibits, which we understand Galderma does not object to. DTX-1008, DTX-1009

and DTX-1283.

THE COURT: Correct. If there's no objection to those?

MS. WILLGOOS: No objection.

THE COURT: All right. Those are admitted.

(DTX-1008, 1009 and 1283 were admitted into evidence.)

MS. GILL: We'd also like to move for the admission of 1014, which we understand Galderma has raised an objection to.

THE COURT: I'm still reserving a ruling on that objection.

MS. WILLGOOS: Thank you, your Honor.

MS. GILL: We'll go ahead and play the clip.

(Videotaped deposition of Robert Ashley played as follows.)

"Question: How long were you employed by CollaGenex?

"Answer: Ten years.

"Question: So from '93?

"Answer: End of -- yeah. '94, yeah.

"MR. SHULMAN: Could you please mark for identification this Ashley Exhibit 1, a copy of U.S. Patent 7,211,267?

"Question: You're the Robert Ashley on this

patent?

"Answer: Yeah.

"Question: Would you turn, please, to column 9. And if you would read to yourself the paragraph that begins at line 9 of column 9.

"Answer: Mm-hmm.

"Question: And in that paragraph, beginning at about line 9, you stated that the tetracycline compound of your invention may be administered by sustained release. Do you see that?

"Answer: I do.

"Question: And in the same paragraph, at around line 14, you stated that further descriptions of methods of delivering tetracycline compounds via sustained release can be found in a patent application entitled Controlled Delivery of Tetracycline and Tetracycline Derivatives filed on April 5th, 2001, and assigned to CollaGenex. Do you see that?

"Answer: I do.

"Question: In the sentence beginning at line 19 of column 9, you incorporated by reference the entirety of the identified controlled delivery application into this specification of the '267 patent; correct? Is that correct?

"Answer: It says, 'The aforementioned

application is incorporated herein by reference in its entirety' --

"Question: Okay.

"Answer: -- which presumably means what you said, yes.

"Question: All right. And in the sentence beginning at line 21 of column 9, you stated that 40 milligrams of doxycycline could be administered in the controlled delivery formulation over a 24-hour period of time; correct?

"Answer: Yeah, what it says here is, for example, 40 milligrams of doxycycline may be administered by sustained release over a 24-hour period.

"Question: Okay. Now, let's mark for identification as Exhibit No. 2, Ashley Exhibit 2, a provisional patent application bearing production numbers MYLDJ2223 through 46.

Let me start over again. Is Exhibit 2 the controlled delivery application that you incorporated by reference into the '267 patent?

"Answer: I just wanted to make sure that this is an accurate reference here.

"What column are we in?

"Question: Column 9, sir.

"Answer: Column 9. I'm sorry.

"Yes. The document says that this patent application was incorporated here in by reference in its entirety, whatever that exactly means.

"Question: Okay. So Exhibit 2 is the referenced document in Exhibit 1; correct?

"Answer: That's what it says, yes.

"Question: And in this paragraph that begins at line 15 on page 2 of Exhibit 2, you state that these conventional tetracycline compositions were required to be taken or administered every three to six hours; is that correct?

"Answer: For those tetracyclines with a short serum half life, that sentence is accurate. This short serum half life requires or required the conventional compositions to be administered often, for example, every three to six hours. It wasn't always true, but...

"Question: Okay. But the conventional tetracycline compositions that you are speaking of here in the paragraph that begins at line 15 are those which have a short serum concentration half life; correct?

"Answer: No, not necessarily. It wasn't true of all of them. I don't know, I'm not a pharmaco kineticist. So there was a range of -- or there is a range of administered times and doses depending on what one's objective is for administering the drug. One example would

be that, for those tetracyclines with a short serum half life, they would have to be administered often if they were cleared quickly. For example, every three to six hours.

"Question: Okay. And that's the direct opposite of the release profile that you wanted to achieve with your invention of Exhibit 2; correct?

"Answer: Well, the objective of the invention was to define a pharmacokinetic profile which avoided spikes of concentration and diminutions of concentration. So in my view, the invention was the notion of a flat or relatively flat release profile or relatively flat pharmaco serum profile -- pharmacokinetic profile -- I didn't know how we were going to get there, but a relatively flat pharmacokinetic profile of serum concentration. But the direct opposite is probably a little aggressive as a statement. But the objective was to avoid those spikes.

"Question: And to flatten out the curve?

"Answer: And to flatten out the curve, yeah.

"Question: Okay. Now, you mentioned just a moment ago in your answer that you didn't know how you were going to get there. What did you mean by that?

"Answer: I had no idea what -- or no meaningful idea what composition might achieve that objective. Nobody had ever tried it before, as far as I knew.

"Question: Okay. Do you describe in this

application formulations that will achieve that objective?

"Answer: No.

"Question: Is there enough information in this application to allow a formulator to achieve that objective?

"Answer: No.

"Question: Okay. Would you turn to page 11, please, and read the first full paragraph of that page to yourself.

"Answer: Okay.

"Question: And there you stated that a delayed release agent is an ingredient that prevents the tetracycline compound from being made available to the host until some time after initial administration of the tetracycline composition.

"Do you see that?

"Answer: No. What I see is, a delayed release agent is an ingredient which prevents the active ingredient, for example -- or that is tetracycline in this case -- from being made available to the host until some time after initial administration. I guess that's the definition of delayed.

"Question: Okay. And that was your understanding at the time that you filed your declaration in connection with this application?

"Answer: I don't recall specifically what my understanding was at that time.

"Question: Well --

"Answer: I don't know what the phrase -- I don't know specifically what defines a delayed release agent.

"Question: Okay. Did you take issue with the statements in this paragraph on page 11 beginning at line 4 at the time that you filed your application?

"Answer: I don't recall objecting to the statement.

"Question: Okay. And, in fact, you signed a declaration which said that you read and understood the statement; correct?

"Answer: I -- as I said before, I don't recall having signed that, but I presumably did.

"Question: Okay. Would you turn to page 7 of your application, please. Would you read the first paragraph on the page to yourself.

"Answer: Okay.

"Question: Are we on the same -- you're on page 7; right?

"Answer: This says page 7.

"Question. Okay. Great. You refer in that first paragraph to the G.I. tract and, in particular, to the

upper portion of the G.I. tract as opposed to the small intestine. Do you see that?

"Answer: That's the last part of that last sentence, yes.

"Question: According to your understanding, what is the upper portion of the G.I. tract? What does it include?

"Answer: Oh, I'm not a -- I'm not a medical doctor. I don't know what the definition specifically of the upper portion of the G.I. tract would be.

"Question: Well, I'm not asking you for a medical definition. I'm just asking for your understanding.

"Answer: Those portions of the G.I. tract opposed to the small intestine.

"Question: So does it mean everything, so to speak, north of the small intestine?

"Answer: Distal.

"Question: I'm sorry?

"Answer: Yes, before the small intestine.

"Question: So do you understand what figure 1 depicts?

"Answer: Figure 1, I -- I understand what it's trying to depict, yes.

"Question: Okay. And what is the spiked curve

that's entitled "instantaneous release?"

"Answer: Well, my understanding of this would be that these are just hypothetical, wholly hypothetical, profiles of release of hypothetical -- it's not even that. I mean, they're just curves which show serum concentrations over time.

"Question: For three different components of a composition?

"Answer: That being completely hypothetical curves.

"Question: For three different components of a composition, sir?

"Answer: Yeah, I think they're just three curves of different serum concentrations over time which are named in this way here.

"Question: Does figure 1 depict a tetracycline release profile that utilizes a combination of three different controlled release agents that are associated with a tetracycline compound in a composition according to your invention?

"Answer: Not really. It shows three different hypothetical curves of serum concentration over time for three things which are just called different things.

"Question: Would you turn to page 7.

"Was the following statement true when you

signed your declaration: Quote, 'figure 1 depicts a tetracycline release profile utilizing a combination of three different controlled release agents which are associated with a tetracycline compound in a composition according to the present invention?'

"Answer: I think that it depicts three different potential tetracycline release profiles. I agree. And one could interpolate a flat profile, which was what this composition -- or what this patent was describing was the notion of a flat pharmacokinetic profile. It is an entirely hypothetical description of how one would get there.

"Question: Would you turn to page 16, please?

"Answer: Maybe I said that in here somewhere. I don't know.

"Okay.

"Question: And if you would read to yourself the paragraph that begins at line 9.

"Answer: I read it.

"Question: Is it correct that at the time you filed this application you preferred that at least 50 percent and more preferably at least 80 percent of the tetracycline in the composition be release in the upper GI tract?

"Answer: Clearly at the time this was written,

that was the -- that was a suggestion for -- well, not a suggestion. Maybe a preferred outcome. However, I didn't know whether that was a necessary outcome.

"Question: Okay. But it was a preferred outcome, as stated here?

"Answer: It states what it states.

"Question: Is that correct?

"Answer: It's correct it states what it states. It states that it's preferred that at least 50 percent and more preferably, greater than 80 percent of the tetracycline in the composition be released in the upper GI tract.

"Question: And if I have done my math correctly, this means that the remainder of the tetracycline in the composition would be release in the lower GI tract; correct?

"Answer: How are we defining upper GI tract and lower GI tract?

"Question: Well, you defined it for me earlier, I believe. You said the upper GI tract is above the small intestine. Do you recall that?

"Answer: I recall that, yes.

"Question: So if I've done my math --

"Answer: That would be -- that would be a reasonable conclusion to draw from this statement that the reciprocal is true. I agree.

"Question: What information did you have that led you to put the lower limit at about .1?

"Answer: Well, preferably put, about .3.

"Question: Well, I want to speak about the .1 first. We'll get to the .3, I promise you.

"Answer: Good.

"The objective was to deliver a sufficient dose to be effective in a cumulative sense.

"Question: What do you mean by a cumulative sense?

"Answer: Over a period of 24 hours. That's defined typically by the area under the curve, in my understanding. So our objective was to deliver a dose which was sufficient to be effective over the period of 24 hours or whatever and yet did not exceed the antimicrobial threshold. And so that was where this definition of the range of dose and the preferable range of doses came from.

"Question: Okay. And what work or research or information did you have available to you that allowed you to state that .1 was the -- or about .1 was the lower limit for the effective amount of the drug?

"Answer: Well, the data that existed were those data with Periostat. And the data from the clinical development of Periostat suggested, for example, that a 20 milligram once-a-day dose was insufficient for affecting

periodontitis.

"Question: So did there come a point in time when CollaGenex decided that it did want a once daily 40 milligram dosage form of doxycycline?

"Answer: My recollection is yes.

"Question: Okay. And at what point in time did CollaGenex decide that, hey, this is something we'd like to develop?

"Answer: I really don't recall.

"Question: Was it before or after you filed this application in April of 2001?

"Answer: Oh, before, I would --

"Question: How long before?

"Answer: I don't recall.

"Question: Was it before CollaGenex ever contacted Shire for assistance in connection with formulating a once daily 40 milligram dosage form?

"Answer: I don't recall, but almost certainly, yes.

"Question: Were you the person who came up with the idea that it would be useful to have a once daily formulation of doxy?

"Answer: I believe so. However, that step, for want of a better word, is not particularly interesting. It's obvious in and of itself.

"Question: Well, was Faulding trying to develop a once daily formulation or a different twice daily formulation or what?

"Answer: Just different. We would experiment or they were experimenting as to whether it was possible to alter the really -- alter the pharmacokinetic profile of doxycycline, as I described, without altering its efficiency, that could have released could have resulted in a once-a-day formulation. I suppose, that might have been one of the objectives.

"Question: Okay. Now, the -- if you'd pull out Exhibit 1, please, which is your '267 patent. Column 9, in the paragraph that begins at line 9, discusses the sustained release or controlled delivery of tetracycline.

"Do you see that?

"Answer: Um-hmm.

"Question: And in the last sentence of that paragraph, you give an example of the amount that may be administered by the sustained release over 24 hours, namely, 40 milligrams. Do you see that?

"Answer: Um-hmm.

"Question: How did you come up with that 40 milligrams amount?

"Answer: Because that was the total administered dose for Periostat, for example. I didn't

know whether that was going to work in a sustained release formulation or whatever, in a -- I don't know whether that was going to work in order to achieve the objectives of the invention, but obviously that's one --

"Question: Okay.

"Answer: -- example of a dose which one could administer.

"Question: And --

"Answer: It was a dose we knew already was safe, and that was really important.

"Question: And that you learned from the Periostat data, so to speak?

"Answer: Correct.

"Question: And, similarly, these blood serum concentration levels that we looked at earlier on whatever page it was, page 5 of Exhibit 2, also were based on your experience with Periostat; correct?

"Answer: As I recall those, yes. Certainly, the top level.

"Question: Let's mark as Exhibit 3 a document bearing production numbers SUP 15508 through 509.

"I understand. But the December 18th e-mail --

"Answer: Right. The December 18th e-mail.

"Question: -- is from Woody Bryan to you, correct?

"Answer: It certainly appears to be, yes.

"Question: And he states in the e-mail, 'thanks again for the opportunity to discuss CollaGenex's interest in once-per-day dosage form for doxycycline hyclate.'

"Does that refresh your recollection that, as of December 2000, CollaGenex was interested in a once daily formulation of doxy?

"Answer: Certainly what it says.

"Question: Okay. But do you recall -- even though you don't recall the call, do you recall that the objective of the program early on with Shire was to develop a once-per-day dosage form that can meet the bioequivalence criteria in comparison to the 20 milligrams twice-a-day dosage form?

"Answer: That certainly looks how Woody interpreted our objectives. I must admit, I don't recall having said that, but that's how Woody interpreted it.

"Question: And he also said that one of the objectives was, given that the half-life of doxycycline is inherently 18 hours, the release profile would potentially only need to be four to eight hours. Do you see that?

"Answer: That, again, is what Woody has said in this document, yes.

"Question: Okay. And point number 4 here is, 'it is believed that doxy is only absorbed in the upper GI

tract and released lower in the colonic region is not desired.'

"And that's consistent with what you told me earlier; correct?

"Answer: Right.

"Question: Is that correct?

"Answer: The literature suggested that at the time, yes.

"Question: Okay.

"Answer: And as I mentioned earlier, release in the colon was not a good idea.

"Question: Let's mark as Exhibit No. 4 a document bearing production numbers SUP 36372 through 83.

"According to the first paragraph of this agreement, CollaGenex asked Shire Laboratories to conduct a feasibility study to evaluate the application of Shire's Microtrol technology with doxycycline as a line extension of CollaGenex's Periostat for the indication of periodontitis. Do you see that?

"Answer: I do.

"Question: Okay. And is it correct that, according to this agreement that you signed on behalf of CollaGenex, what CollaGenex desired was a controlled release oral solid dosage form that can deliver up to 40 milligrams of doxycycline over a six to eight hour period of time?

"Answer: In a dosage unit of reasonable size and appearance.

"Question: Yes.

"Answer: That was clearly one of the objectives of this development agreement, yes.

"Question: Okay. And the first sentence refers to Shire's Microtrol technology; do you see that?

"Answer: Um-hmm.

"Question: What was that, according to your understanding?

"Answer: I don't recall the details of Shire's Microtrol technology. Shire had a numerous technologies and, most importantly to us, a bunch of expertise in formulation development. And so Microtrol was, as I recall, one of -- they had a product called Carbatrol, I think, so that was one of the technologies which they had.

"Question: Okay. Now, under the heading stage 1 on page 1, it says that the primary objective in stage 1 will be to formulate and test IR and DR beads for use in a capsule dosage form utilizing Shire's Microtrol technology. Do you see that?

"Answer: Yeah. It says the primary objective of stage 1 will be the development and testing of immediate release and delayed release beadlets for utilization in a composite capsule dosage form, using Shire's Microtrol

technology.

"Question: Did Shire contribute in any way to do the information that you set forth in your provisional patent application, Exhibit 2?

"Answer: Not that I recall, no.

"Question: Okay. So everything in here was your ideas?

"Answer: Ever in that pre -- well, as I recall, yes.

"Question: Okay. And looking at Exhibit No. 1, column 9 --

"Answer: One was the '267 patent?

"Question: Yes, sir. Looking at column 9, the paragraph that begins at line 9. Was it your idea, as opposed to someone at Shire's, to include in this paragraph the exemplary sustained release formulation that contains 40 milligrams of doxycycline?

"Answer: Do you mean the line, for example, 40 milligrams of doxycycline may be administered by sustained over a 24-hour period?

"Question: Yes, sir.

"Answer: That was one example of how one would achieve the objectives of this patent, yes. And I have no reason -- it's -- in and of itself, 40 milligrams would be certainly the dose which one would try first.

"Question: Okay. So that was your idea?

"Answer: The idea was to achieve -- I believe that you needed to administer 40 milligrams of doxycycline or something around that dose in order to be -- over a 24-hour period in order to be effective.

"Question: Okay. And that was an idea that you came up with as opposed to having been told that by someone at Shire?

"Answer: I don't recall Shire -- a discussion with Shire. I recall Shire suggesting that we may need -- if we wanted to achieve the objectives which were laid out, laying within those boundaries over a sustained period, that we may need to deliver more than that.

"Question: Okay.

"Answer: But my objectives in the patent at least was to find a way of delivering 40 milligrams, or somewhere around a dose of 40 milligrams of doxycycline, to get that area under the curve without the spikes and troughs so we'll have a flatter PK profile.

"Question: Okay. Now, earlier today you mentioned that, according to Shire, they thought that to achieve the desired PK profile, they may have to use more than 40 milligrams of doxy in the formulation. Do you recall that?

"Answer: I recall there being discussions about

that.

"Question: And can you tell me what your understanding is of why Shire believed that perhaps more than 40 milligrams would be necessary?

"Answer: I don't recall specifically, but I do recall a discussion about that.

"Question: And what about that discussion do you recall?

"Answer: Just the discussion of the need potentially to have a larger dose to achieve the serum concentration parameters which we were preferring.

"Question: Did anyone explain why there might be a need for a higher dosage to achieve those serum concentrations that you desired?

"Answer: I don't recall. I don't recall the discussion. But I do recall a discussion on that topic.

"Question: Okay. And what was CollaGenex's reaction to this suggestion that you might have to go above 40?

"Answer: Well, if that was the case, that would complicate our clinical development programs then.

"Question: Why would that be the case?

"Answer: Because we wouldn't have been able to rely so much on the fact that we'd already demonstrated that 40 milligrams every 24 hours with Periostat was safe. So we

would certainly prefer that not to have been the case, but if -- as I say, we weren't formulation people, so maybe that was the only conclusion. I don't know.

"Question: Let me back up. Look at Exhibit 11, the second e-mail on the first page, the third paragraph. Second sentence. It states that, 'this is not necessarily accurate as we were aware that region specific absorption may very well be an issue based on comments from CollaGenex, voiced by Rob Ashley during kickoff meeting and during face-to-face meeting with Shire team at the time of prototype -- prototype selection, and the Faulding report, albeit late in the process.'

Do you have any reason to doubt the truth of what Mr. Bryan said here, namely, that he had been aware that region specific absorption may very well be an issue based on comments from you and during the face-to-face meeting with the Shire team at the time of the prototype selection as well as the Faulding report?

"Answer: Yeah, I don't know what Woody was thinking.

"Question: That wasn't my question. The question is do you have any reason to doubt that Mr. Bryan believed what he stated here in the second sentence of the third paragraph of the second e-mail on page 1 of Exhibit 11.

"If you have a reason, tell me about it. If you don't, you can say no.

"Answer: No, I have no -- I -- I have no reason to think that this isn't what Woody thought.

"Question: Was Faulding's approach very different, in your view, than the approach that Shire took?

"Answer: Yes. I think that their -- yes. Faulding's approach was very different.

THE COURT: What's going to be next?

MS. GILL: Your Honor, Richard Chang. This clip is about 50 minutes, so it might be appropriate to break for lunch.

THE COURT: 50? 50?

MS. GILL: Yes.

THE COURT: We'll take our lunch break and we'll begin with that. When we get back, we'll see you about 1:35 or thereabouts.

(Luncheon recess taken.)

AFTERNOON SESSION, 1:45 P.M.

THE COURT: Good afternoon. Before we move on with the testimony, let me give you my rulings on the objections from the plaintiff to the two exhibits that we discussed this morning, DTX-1014 and DTX-1085. I'm going to overrule the objections and allow the documents to be admitted.

DTX-1014 appears to be an e-mail chain amongst Supernus representatives. Supernus is a party here. Therefore, in this case, it looks as if these are non-hearsay and therefore admissible as party admissions. The foundation appears to be established in that the document appears to be produced by Supernus, and there's certainly no basis in the record to conclude otherwise. The Court, of course, will give it the weight it deserves along with everything else, including the Ashley deposition excerpts.

And with respect to DTX-1085, it appears to be an e-mail chain among CollaGenex and Shire, the predecessor in interest to the parties in this case, Galderma, some of the parties in the case, Galderma and Supernus, respectively. It appears again to have been produced by Supernus in this case. Therefore, it appears the foundation was adequate and, again, the Court will admit it, give it the weight it deserves in connection with all the other evidence.

With that, we'll hear I believe next from Dr. Chang; correct? All right. You may proceed.

MS. WILLGOOS: Your Honor, we have one additional exhibit that was part of our counterdesignations for Chang that's not in the defendants' exhibit binder.

THE COURT: If you want to pass that up, that's

fine.

(Ms. Willgoos handed an exhibit to the Court.)

MS. GILL: Your Honor, Mr. Chang is the first named inventor of the Chang patent, and also at this time we'd like to move into admission DTX-1071, DTX-1079, DTX-1081, DTX-1086, DTX-787, DTX-1088, DTX-1090, DTX-1094, DTX-1095, DTX-1283, DTX-1285, DTX-1294, and DTX-1298.

MS. WILLGOOS: No objections, your Honor.

THE COURT: Those are all admitted.

(The above-referenced exhibits were admitted into evidence.)

MS. GILL: We're going to start playing the clip.

THE COURT: All right. Mr. Golden, if you want to down some of the lights, please.

(Videotaped deposition of Richard Chang played as follows.)

"Question: Would you state your full name, please.

"Answer: My full name is Richard Rongkun Chang.

"Question: So you were with Shire/Supernus from approximately 1997 until 2009?

"Answer: That's right.

"Question. Okay. And at Shire, you did do work with capsules containing beads for extended release

products; correct?

"Answer: That's correct.

"Question: Okay. And did the Adderall product that you worked on contain immediate release beads?

"Answer: Yes.

"Question: Did it contain delayed release beads?

"Answer: Yes.

"Question: Did it contain any other types of beads?

"Answer: No.

"Question: Apart from the Adderall XR, what other bead containing capsule formulations did you work on at Shire?

"Answer: Bead containing -- doxycycline.

"Question: Okay. Any others?

"Answer: That -- that's about it.

"Question: Okay. And was the Carbatrol product, did it have a commercial name or was it called Carbatrol?

"Answer: Carbatrol.

"Question: And was the Carbatrol product a capsule with beads in it?

"Answer: Yes.

"Question: And were the beads in the Carbatrol

product, did they include immediate release beads?

"Answer: Yes.

"Question: Did they also include delayed release beads?

"Answer: There are three types of beads in the capsule.

"Question. Okay. Was -- well, one of the types was immediate release; correct?

"Answer: Mm-hmm.

"Question: Was a second type delayed release?

"Answer: Yes.

"Question: And what was the third type?

"Answer: Sustained release, with delay.

"Question: Okay. Now, you have heard of the term Microtrol technology?

"Answer: Yes.

"Question: What does that mean?

"Answer: It's a general term to -- to describe the dosage form, the dosage form that Shire has. It is beads in the capsule, we call Microtrol.

"Question: Okay. And when you use the Microtrol technology, can you have all of the same type of beads in a capsule, like IR beads?

"Answer: Yes. It's possible.

"Question: Okay. Or you can have combinations

of IR and DR as well as perhaps others?

"Answer: That's right.

"Question: Okay. Did the Adderall XR product use the Microtrol technology?

"Answer: That Microtrol is just for -- for -- for business development purpose, just to try to educate the client what kind of dosage form we can develop. Not actually is a fixed technology.

"Question: Okay. But to the extent -- you described, if I understood you correctly, Microtrol technology as beads in a capsule?

"Answer: That is -- that's right, just -- just to give a name to it -- to it. It is beads in capsule.

"Question: Okay. So with that understanding, Adderall did use beads in a capsule, which is the generic description of Microtrol?

"Answer: That's correct.

"Question: And so did the doxy project?

"Answer: That's correct.

"Question: And so did the Carbatrol project?

"Answer: That's correct.

"Question: Was Carbatrol develop at Shire?

"Answer: Yes.

"Question: Now, did there come a point in time when you learned that Shire and CollaGenex had entered into

an agreement concerning the development of a once-a-day 40-milligram dosage form of doxycycline?

"Answer: 2001. 2002, I don't --

"Question: But you learned that they entered into an agreement?

"Answer: That's right.

"Question: Let me hand you what was marked as Raoufinia Exhibit number 1.

"Answer: Okay.

"Question: It has the AR numbers on it, his initials.

"Have you ever seen this development agreement before?

"Answer: I sure have.

"Question: Okay. If you look at the first paragraph on the first page, and you can just read it to yourself, it says there that: CollaGenex asked Shire Labs to conduct a feasibility study to evaluate the application of Shire's Microtrol technology with doxycycline as a line extension of CollaGenex's Periostat for the indication of periodontitis.

"Do you see that?

"Answer: Yes.

"Question: And it goes on to say in that same paragraph that: What CollaGenex desired was the development

of a controlled release oral solid dosage form that can deliver up to 40 milligrams of doxycycline over a six to eight-hour period of time.

"Do you see that? Do you see that?

"Answer: Yes.

"Question: To your knowledge, was any work done at Shire on formulating doxycycline before the agreement, Raoufinia Exhibit 1, was signed?

"Answer: No.

"Question: No work was done?

"Answer: No work was done.

"Question: Okay. Did you participate in the drafting of this agreement?

"Answer: Definitely, yes.

"Question: Okay. Now if you could go back to the agreement.

"Answer: Mm-hmm.

"Question: Raoufinia Exhibit 1. I am going to refer to the Raoufinia exhibits as AR because Raoufinia is a mouthful.

"If you turn to page one of AR, in Section A entitled, Stage 1, the agreement states that: The primary objective of Stage 1 of the feasibility study was to develop IR and DR beadlet formulations for inclusion in a combined capsule dosage form using the Microtrol technology.

"Do you see that?

"Answer: Yes.

"Question: And is that what CollaGenex wanted from Shire, to your understanding?

"Answer: That's correct.

"Question: Okay. If you turn to the top of page 2 of this agreement, and just read that paragraph to yourself, the very first paragraph.

"You can -- you are always free to read whatever you want. Is that okay?

"In the first paragraph, it states that: During Stage 1, CollaGenex and Shire contemplated that formulations of these IR and DR beadlets would be selected for a pilot PK study to be performed in humans.

"Do you see that?

"Answer: Yes.

"Question: And was that study referred to internally at Shire as the pilot PK study?

"Answer: That's correct.

"Question: If you look at the fourth bullet point under heading 5 on page 2 of this exhibit, No. 6, it states that: In silico modeling will also take place after the receipt of the first PK study results prior to the start of the second PK study.

"Do you see that?

"Answer: Yes.

"Question: So is it correct that as of March 6th, 2002, CollaGenex and Shire had agreed that in silico modeling of various ratios of IR to DR bead formulations would take place after receipt of the results from the pilot PK study?

"Answer: Yep.

"Question: Okay. And the PK study results were a necessary input to perform the in silico modeling; is that correct?

"Answer: Yes.

"Question: Okay. So are you saying that because the window of -- of absorption is so narrow --

"Answer: That's right.

"Question: -- you couldn't use the IR all by itself or any of the DRs all by themselves?

"Answer: I -- I am saying because the absorption window is so narrow, all the DRs going to lose -- lose bioavailability significantly.

"Question: They're going to lose what?

"Answer: Bio -- bioavailability significantly, but you use IR, you lose -- you lose the duration.

"Question: Okay. Did you have any ideas of what that combination should look like as of the time you wrote this e-mail, in early October of 2002?

"Answer: Just -- at the time maybe the concept is very vague. Maybe it is IR combination and not DR beads. Most likely it is DR one bead.

"Question: Most likely it's?

"Answer: DR 1 beads.

"Question: DR 1?

"Answer: Mm-hmm.

"Question: Did you have in mind as of October 10th, 2002, any particular role of IR to DR 1 beads?

"Answer: No, I don't.

"Question: Now, Doctor, Raoufinia's e-mail of October 16th, he says that -- it's on the last page of the document under the heading goals, that any of his goals is to model IR/DR bead formulations that will yield a Cmax that is less than 750 nanograms per milliliter and a Cmin that is greater than 300 nanograms per milliliter.

"Do you see that?

"Answer: Yes.

"Question: Did CollaGenex specify that range of Cmin to Cmax?

"Answer: CollaGenex have previous experience with the Periostat, so they have a better knowledge and understanding of the -- the PK performance of the doxycycline. So this is initial target goal for -- so they set for us.

"Question: By CollaGenex?

"Answer: By CollaGenex.

"Question: Okay. So CollaGenex initially set this range of Cmin to Cmax that's reported here on the last page of Exhibit --

"Answer: That's right.

"Question: -- 3; correct?

"Answer: Yes. Correct.

"Question: Okay. So was one of the goals of the modeling to identify an IR/DR formulation that approximated the steady state blood levels of doxy obtained from the twice daily administration of Periostat?

"Answer: You can say that.

"Question: Pardon?

"Answer: You can say that.

"Question: Yes?

"Answer: Answer. Yes:

"Question: Okay. Did CollaGenex ever tell you what the desired plasma profile was for the product that you were developing on their behalf?

"Answer: Yeah. Just -- I say this just before, CollaGenex have prior experience with the doxycycline, so they have better understanding of the plasma level of the doxycycline. So when we sign a contract, they -- they already inform us, they give us the very vague target.

"Question: And what was the initial target they gave you?

"Answer: They just say .1 microgram per ml to one -- one microgram per ml.

"Question: Or -- that's another way of saying that is 100 nanograms to 1,000-nanograms per ml?

"Answer: That's right.

"Question: Okay. Did they tell you that they want to mimic the bid dosing of Periostat?

"Answer: That nobody needs to tell us because that's golden guide. It is a guide. Is -- everybody knows this is -- now you have products, dosing twice a day, so you dose twice a day. Now you want to convert to once a day, you supposed to have once a day profile similar to that profile that you -- you have never confidence to go into the clinical study.

"Question: So one of the goals from the outset was to create a once-a-day product that would mimic the dosing of the twice-a-day product?

"Answer: That's --

"Question: And they also gave you this broad range of 100 nanograms to 1,000 nanograms per milliliter as the Cmin to Cmax?

"Answer: That's correct.

"Question: Okay. If I understand you

correctly, what you are saying is the .1 to 1 was the broad band?

"Answer: Mm-hmm.

"Question: And then the .3 to .75 was the narrow preferred band that CollaGenex identified?

"Answer: I just say it is not necessary come from the CollaGenex.

"Question: So was it your understanding in the summer of 2002 that CollaGenex had specified that its preferred range for Cmin to Cmax was in the neighborhood of .4 to .7 micrograms per ml for 24 hours, and an AUC that was consistent with the bid formulation?

"Answer: Yes, from this e-mail, yes.

"Question: Let's mark as Exhibit 12 a one-page document bearing production number SUP 12680.

Is this a copy of an e-mail from Michele, Coulaloglou, Coulaloglou, or something like that --

"Answer: That's right.

"Question: -- to you and others, dated October 23rd, 2002?

"Answer: Yes.

"Question: Okay. And she was providing an update on the doxy project after meeting with you that morning?

"Answer: Yes.

"Question: Okay. And on the IR pellet formula, she says that the sugar spheres used are 30/35 mesh, 500 to 600, is that microns?

"Answer: Yes.

"Question: Comma, like used in Adderall XR.

"Do you see that?

"Answer: Yes.

"Question: Is it correct that the IR doxy pellets were sugar spheres on which the doxy was coated?

"Answer: That's right.

"Question: Okay. And as reported here, were the sugar spheres used for the IR doxy pellets the same as those used for the IR pellets in the Adderall XR product?

"Answer: Yeah, the core -- the core substance is the same as the Adderall XR.

"Question: Now, under DR pellet formula in Exhibit 12, it says that: 'The formula for the enteric coating will be IMB 444 or DR 1, which uses Eudragit or Eudragit, L30D55; is that correct?

"Answer: Correct.

"Question: And as of 2002, Eudragit L30D55 was an enteric pharmaceutical coating that had long been available from Rohm; correct?

"Answer: That's correct.

"Question: Was Eudragit L30D55 used in

Adderall?

"Answer: That's correct. We used the -- the L30D55 for Adderall XR.

"Question: For Adderall XR.

"Answer: That's right.

"Question: To coat the delayed release beads?

"Answer: That's correct.

"Question: Later in this e-mail, there is a heading which says 'bead ratio and capsule strength.' Do you see that?

"Answer: Yes.

"Question: And it says quote, 'these will be adjusted to provide the target plasma profile, et cetera, et cetera.

"What was the target plasma profile as of October 23rd, the date of this e-mail?

"Answer: Still is .1 microgram per mil to 1 microgram per mil.

"Question: With a preferred narrower range of .3 to .75?

"Answer: That's right. That's right.

"Question: Let me ask you to look at Dr. Raoufinia's Exhibit 12.

"Answer: Yes.

"Question: Did you receive a copy of this

e-mail with the attachment from Dr. Raoufinia on or about November 6th, 2002?

"Answer: Yes.

"Question: Okay. And did you read the in silico modeling report that Dr. Raoufinia attached to the e-mail?

"Answer: Yes.

"Question: Okay. Let me ask you to look at Raoufinia Exhibit 15. And I will just tell you that that's a copy of the in silico report that was sent to CollaGenex.

"Answer: Yes.

"Question: Okay. Did you receive a copy of this document on or about November 15th, 2002?

"Answer: Yes.

"Question: And it says on the first page that this report was forwarded to CollaGenex on Thursday the 14th of November. Do you see that?

"Answer: Yes.

"Question: And were you aware that the report was being forwarded to CollaGenex?

"Answer: That's correct.

"Question: Now, why were 45 milligrams doxy formulations examined as part of this in silico modeling study?

"Answer: We try to show, we can vary IR and DR,

the ratio, and on top of that, we can vary a strength to -- to change the profile.

"Question: Right.

"Answer: That's it.

"Question: The agreement that was entered into, the basic agreement that we looked at earlier, called for the development of a 40 milligram formulation; correct?

"Answer: That's correct.

"Question: Okay. And so why were you presenting at least modeling results on a 45 milligram formulation?

"Answer: It give the client more opportunity to select.

"Question: Okay. And apart from the six ratios that are reported in this modeling report, were there any other ratios obtained in the modeling effort that came close to approximating the .3 to .75 target range, to your knowledge?

"Answer: To my knowledge, all this is formula for presented here, is very close to the target. It can be selected as the -- the candidate to continue for development.

"Question: Okay. And is it correct that in this report there is no data on a 75/25 formulation?

"Answer: I already said to you that the ratio

between IR and DR is selected by the Arash, to put into the report.

By Arash Raoufinia to put into the report. Actually, he did much more than this.

"Question: Okay. Now, for the 40 milligram dosage form that is examined in this report, the ratios used are 95 to 5, IR to DR, 90 to 10 and 80 to 20; correct?

"Answer: Yes.

"Question: There is nothing lower than 80 to 20 for the 40 milligram version; correct?

"Answer: In this report, yes.

"Question: And for the 45 milligram dosage form, the only ratios used were 90/10, 85/15, and 70/30. Correct?

"Answer: That's right.

"Question: Okay. Let me mark as Exhibit No. 13 a two-page document bearing production numbers SUP 12723 through 23.

Now, in the second sentence of your e-mail in Exhibit 13, you wrote that, hopefully by some time next week you can get the input and approval from CollaGenex about the ratio of IR and DR beads so that the project can be continued.

"Do you see that?

"Answer: Yes.

"Question: Why did you want CollaGenex to tell you what ratio of IR to DR beads to use?

"Answer: Maybe you not familiar with the -- the contract R&D business.

"Maybe you don't understand the contract -- contract R&D business.

"Question: Okay.

"Answer: The client is our God, so every time you need to ask them to approve of something. You -- every decision you make, right, you try to influence, but sometimes they have their own idea. So every time you just back and forth and negotiate something workable.

"Question: Dr. Chang, in connection with that initial pilot PK study that we spoke about earlier, one IR bead formulation was tested as well as three DR bead formulations. Correct?

"Answer: That's correct.

"Question: And the DR bead formulations were known as DR 1, 2 and 3; correct?

"Answer: That's right.

"Question: Let me ask you to look at Raoufinia Exhibit 17. Do you recall before the break we looked at some document you wrote where you said there would be a need for a new business agreement to pursue the -- the project?

"Answer: That's right.

"Question: And is Exhibit 17 a copy of the new business agreement which was entered into in December of 2002 to permit further development of the product?

"Answer: That's correct.

"Question: Okay. And the caption of -- of this program expansion, Exhibit 17, is R&D demonstration encapsulation and GMP supply manufacturer for doxycycline, pulsatile, P-U-L-S-A-T-I-L-E, release capsules, (PR) in a human pilot biostudy for CollaGenex pharmaceuticals.

"Do you see that?

"Answer: Yes.

"Question: And the pulsatile release capsules, that was a terminology that was used at Shire to describe the Adderall XR product; correct?

"Answer: That -- that's correct.

"Question: Is it correct, sir, as reported in this agreement on the bottom of page 1, that based on the in silico modeling results that we went over earlier today, CollaGenex requested that Shire make a 40 milligram doxy capsule formulation that contained IR and DR beads in the ratio of 75 to 25?

"Answer: That's correct.

"Question: Do you know why CollaGenex chose this 40 milligram 75/25 formulation rather than one of the formulations set forth in the in silico modeling report that

we looked at earlier?

"Answer: This thing, right. This -- this, so many option there. One option is their strength. You can increase 45 milligram to 45 milligram to gain some advantage about the -- the plasma level. You can increase -- you can increase the Cmax, increase the Cmin, and by doing that, 40 -- 40 to 45 milligrams change.

And also you can have a non-option, to change IR and DR ratio, to -- to manipulate it, the Cmax and the Cmin. So this all related. So you need to do some trade-off to select the right strength -- not the right strength, the strength you like. And also the IR, the strength, the strength you like, or the IR/DR ratio you like.

"Question: Okay. So these are parameters that you can simply choose between to get the plasma profile you want?

"Answer: That's correct.

"Question: And do you know why CollaGenex chose the 40 milligram 75/25 formulation?

"Answer: You keep asking -- keep asking 40 milligram, 45 milligram, and different ratio. That's -- I tell you it is not much difference, just the trade-off here and there. So, for example, right, you change the 40 to 45. Doesn't mean you, you go increase the Cmax more, but the Cmax, you increase the Cmax, you have a chance to fail the

top limit.

"Question: The 1?

"Answer: The 1, yeah. For big, big pocket. Then you have a chance, then you have a higher chance to succeed in the Cmin.

"Question: To succeed in the Cmin?

"Answer: Cmin is greater than the .1, or .3, the target limit. That's the advantage.

"For the IR and DR ratio, same thing. You can rationalize this. For IR portion, you can increase it. Then you have higher chances to fail the Cmax limit. Very easy to, to over the Cmax.

"Question: Right.

"Answer: But you, you decrease it, the Cmin, Cmin, you have a chance to fail. So it all just all trade-off. So you give to anybody who know the business, they can combination of all this to pick out one they think is suitable for the product.

"Question: Okay. And do you know why CollaGenex decided that all of the various trade-offs, as you have described it, 40 milligrams formulated at 75/25 seemed to be the best one?

"Answer: That that -- I know they-- for Shire is the contract R&D. We only can provide all option to them. Then based -- based on the data we provide, that I

have a right to choose the -- the formula, ask us to continue.

"Question: Okay. Did CollaGenex express any concerns about going to a 45 milligram dosage form as opposed to a 40 milligram dosage form?

"Answer: That I don't -- I don't remember they expressed their concern. But the -- internally at Shire, at least, we -- we know that 45 is not desirable, because the assembled and absorbed doxycycline can destroy the GI normal, GI normal flora.

"Question: Okay. I'm sorry. I didn't catch all of that. Would you mind repeating it?

"Answer: The 45 milligram up the dose. The -- and also we know, that the doxycycline, lower GI, absorption is very poor. So have chances that some drug residue in the lower GI.

"Question: Residue?

"Answer: Residue cannot get absorbed through the systemic may have the effect on the -- the bacteria normal flora in the gut.

"Question: The normal flora in the gut?

"Answer: In the gut.

"Question: Okay. Do you have any recollection of coming up with the 75/25, 45 milligram formulation before this contract was signed, Exhibit 17?

"Answer: All the -- the decision made, right, all based on all simulation data. Without that data, no -- no one can make up the ratio.

"Question: Do you recall thinking of the 75/25, 40 milligram formulation before CollaGenex selected that formulation as reflected in Exhibit 17?

"Answer: No, I don't remember.

"Question: Do you know who the person was at CollaGenex who made the request that a 40 milligram 75/25 doxy formulation is the one that they wanted to pursue?

"Answer: I don't remember. But based on this, this is this contract.

"Question: Based on this contract, you mean Exhibit 17?

"Answer: Yes, that's right.

"Question: Let's mark for identification as Exhibit 14 a document that we received last night. It has production numbers SUP 54017 through 25.

"Okay. And what is this document?

"Answer: Look like it is a report for simulation.

"Question: Let me show you Raoufinia Exhibit 18.

"Answer: Yes.

"Question: Which contains a substantial portion

of what appears in Chang Exhibit 14. Let me hand that to you.

"Basically, what appears in Raoufinia Exhibit 18 --

"Answer: Um-hmm.

"Question: -- let me just pull that out to assist you -- begins on the second page of Exhibit 14, second paragraph. Do you see that?

"I just want to show you where the portion that was written by Dr. Raoufinia appears in Exhibit 14.

"Answer: Um-hmm.

"Question: Okay? So Dr. Raoufinia said that he wrote Exhibit 18?

"Answer: Okay.

"Question: On the first page of this document, Exhibit 14, the second to last sentence, it says, 'from the modeling results and IR/DR ratio between 70/30 and 80/20, inclusive, perhaps 75/25, is recommended for the proof of concept PK study.'

Do you know who came up with that recommendation?

"Answer: This -- I -- I really cannot say anything. I -- I really am not involved in this -- this report.

"Question: Was Mr. Shah, the formulator,

involved in preparing this report?

"Answer: No.

"Question: And you weren't?

"Answer: I'm not.

"Question: Pardon?

"Answer: I'm not.

"Question: You were not involved?

"Answer: No.

"Question: With respect to the work that you did on the doxycycline project, did you ever believe that any aspect of that work was an invention?

"Answer: Yes.

"Question: Did you believe that .1 to 1 micrograms per milliliter as a Cmin to Cmax was patentable as an invention in your mind?

"Answer: The number by itself is meaningless. But we have data. We have formula, can achieve that -- that -- that plasma profile. That mean a lot.

"Question: Right. You didn't come up with that range for doxycycline, namely, .1 to 1, and that was something that was given to you as a target; right?

"Answer: Yes. Yes, that number come from the -- Bob Ashley, because they have previous experience, but that target is useless. Because they cannot formulate it, a dosage form, can achieve their target.

"Question: Okay. They cannot formulate to achieve this target.

"You didn't come up with the idea of 45 milligrams of doxycycline as the amount to be contained in the formulation; correct?

"Answer: Again, it -- this -- we provide option to the CollaGenex. Is it 40 or 45? You can have more option for the client to select, so I think they have a better chance to continue the -- the -- the development program.

"Not -- 40-milligram we know.

"Question: We know what?

"Answer: We know is ideal. For -- for this part is better in terms of the -- the dose strength.

"Question: Right, but when they came to you initially --

"Answer: It's 40.

"Question: -- and signed the first contract, they wanted a 40-milligram dose?

"Answer: That's right.

"Question. Okay. And they wanted to utilize your bead technology; correct?

"Answer: Yes.

"Question: And they wanted a combined immediate release, delayed release product; correct?

"Answer: Not they wanted, is that we proposed. We know better than the CollaGenex. We proposed IR and DR combination.

"Question: Okay. And did you believe you were a joint inventor of the subject matter claimed in this application at the time that you signed the declaration?

"Answer: Yes.

"Question: Okay. Now, there are three individuals named here, you, Dr. Raoufinia and Mr. Shah.

"Answer: Correct.

"Question: Okay. Among the three of you, who was the first person who first thought of the idea of a once-daily formulation of doxycycline, giving steady state blood levels of a minimum of .1 and a maximum of about 1.0 micrograms per milliliter?

"Answer: Myself.

"Question: That was you? Did you think of that range?

"Answer: That I tell you, the original range is from -- from the -- Bob Ashley. When they give this -- this range, was no meaning, just a -- just a target. But we is the one who developed a product to achieve that -- that -- that target.

"Question: Right.

"Answer: To put some meaning to it.

"Question: I realize you -- you developed the product, the formulation.

"But the idea of developing a once-daily formulation of doxy, giving steady state blood levels of between .1 and 1, came from CollaGenex; correct?

"Answer: How many times I need to say. Yes, this is from -- from there. But the -- but I need to point out this, they couldn't develop product to achieve this goal. Doesn't mean this -- this number is meaningless. I -- we are the -- the development team, develop product to achieve this goal, so to put some meaning to the -- the value.

"Question. Was there any aspect of the invention that was first thought of by either Mr. Shah or Mr. Raoufinia, before you?

"Answer: No, I don't believe.

"Question: So you thought of everything first?

"Answer: Because I get the information first. From -- from the -- the -- line management.

"Question: From the?

"Answer: Line management. Upper management.

"Question: You got what information first from upper management?

"Answer: The -- the contract, the -- all the information from -- from the CollaGenex.

"Question: Uh-huh. So in terms of thinking of the invention, coming up with the idea of the invention, what, in your opinion, did Mr. Shah contribute?

"Answer: Shah -- Shah contribute in the formulation and the process development.

"Question: Okay. What, if anything, did Mr. Raoufinia contribute to coming up with the idea for the invention?

"Answer: Simulation work. All the simulation work, they asked us to -- to have a ratio, which -- first the simulation, to simulate the three IR beads and three DR beads -- three. Three DR beads. That later on have a second simulation to identify the -- the ratio and then the -- the different strength.

"Question: Okay. Among the three of you, who was the person who first came up with the concept of such a formulation having a 3 to 1 ratio of IR to DR portions?

"Answer: The ratio I think is picked by the -- the CollaGenex, but based on our data, all simulation data sent to -- to -- to CollaGenex, and after discussion, they -- they picked the ratio.

"Question: Okay. So is it fair to say that nobody at Shire, to your knowledge, came up with that ratio. That was something CollaGenex picked?

"Answer: It is still the same thing. This --

this is contract -- this is a contract R&D for business. Everything agreed to -- to -- the -- by the client.

"So this information we provide. They will agree to it, then we continue.

So, yes, some -- yes, some -- some sense they agreed to it, 75:25. We continue the program.

"Question: Right, but who first came up with the idea of 75:25? Did it come from the CollaGenex guys or did you propose it to them?

"Answer: At least I didn't propose, so I don't know who proposed.

"Question: You personally --

"Answer: I personal --

"Question: Did not propose 75:25?

"Answer: No.

"Question: Do you know if Dr. Raoufinia proposed 75:25 to CollaGenex?

"Answer: Possible. Because he is the one doing the simulation work.

"Question: But do you know if he did?

"Answer: I cannot be 100-percent sure.

"Question: Okay. Do you know if Mr. Shah proposed 75:25 to CollaGenex?

"Answer: No.

"Question: He did not?

"Answer: No.

"Question: And according a figure 4, the steady state blood levels for doxy obtained from the once daily administration of 40 milligrams of immediate release doxy also fall between .1 and 1.0 micrograms per milliliter; correct?

"Answer: You keep -- your question, yes. The problem is you use 40-milligram IR dose, immediate release dose, you have chances to over one microgram per ml very easily. That -- that's the thing.

"Question: Okay. But according to the data in your patent, the once daily administration of 40 milligrams of immediate release doxy fall between .1 and 1.0 micrograms per milliliter as the steady state blood levels; right?

"Answer: Yeah, I tell you is true, according to this figure, yes, meet the criteria, but don't forget, individual subject, individual subject dosing, you are using the 40 milligrams IR once a day, once daily, the Cmax frequently over one microgram per ml.

"Question: Okay. Now, let's focus on this other range that is recited in the claims, namely, .3 to .8. Okay?

"And let's go back to figure 4. Is it correct that the steady state blood levels for the 80:20 formulation do not fall within .3.8 micrograms per ml?

"Answer: Yeah.

"Question: Is that correct?

"Answer: Yeah. Correct -- missed the Cmin.

"Question: Missed the Cmin.

"Is it also correct that the steady state blood levels for the 70:30 formulation in figure 4 do not fall within .3 to .8 micrograms per ml?

"Answer: Correct.

"Question: Is it also true that the steady state blood levels for the 40 milligram once daily immediate release formulation in figure 4 do not fall within the .3 to .8 micrograms per ml range?

"Answer: Correct.

"Question: And is it true that all of the steady state blood levels for the Periostat twice daily in figure 4 do fall within the range of .3 to .8 micrograms per ml?

"Answer: That's correct.

"Question: Now, let's look at figure 5. In figure 5 in the white squared graph, we have steady state blood levels for the once daily 40-milligram dose of doxy containing the 75:25 ratio; correct?

"Answer: That's correct.

"Question: Is it correct, sir, that according to figure 5, the 75:25 dosage form results in steady state

blood levels that do not fall within the range of .3 to .8 micrograms per ll -- ml?

"Answer: Correct.

"Question: Are you aware of any data in your patent, sir, which shows that from a once daily dosage of 40 milligrams of doxy, the blood levels achieved at steady state all fall between a minimum of .3 and a maximum of .8 micrograms per ml?

"Answer: No.

"Question: Why don't we mark as Exhibit 16 a multi-page document bearing production numbers SUP 14593 through 603.

"Okay. And were you the person who put together this presentation?

"Answer: Yes.

"Question: Okay. Who attended the presentation on behalf of CollaGenex?

"Answer: Bob Ashley.

"Question: So in this slide, you stated that one of the goals of the program was to develop a once-a-day Periostat XR using the Microtrol technology.

"Correct?

"Answer: That's correct. The Microtrol technology in Shire would mean beads in capsule.

"Question: Right. I understand that.

"Then on the next page, you titled the slide 'Approaches to the Periostat XR Formulation Development.'

"Correct?

"Answer: Yes.

"Question: And then you listed three bullet points beneath that; correct?

"Answer: Yes. Let me say it again. This pattern, this here is trying to show the client we are capable, Shire is capable to develop product, and those will have a patent with the -- the product. It is not really associated to -- to doxycycline. Try to -- try to use this technology --

"Question: Well --

"Answer: -- we're using here.

"Question: Was the -- the Microtrol technology was the bead approach; correct?

"Answer: That's right. Beads in capsules.

"Question: Right.

"Answer: These three patents is beads in a capsule.

"Question: Right. And so what you were showing is that you could use and had used the beads in capsule approach to develop drugs in the past; correct?

"Answer: That's right.

"Question: Okay. And what you were telling

them here is you could use a beads in capsule approach to the Periostat XR formulation development?

"Answer: That's right.

"MR. SHULMAN: Let's mark as Exhibit No. 20 a document bearing production number SUP 27363.

"Question: The first e-mail in the chain on this exhibit is dated May 24th, 2005. Do you see that?

"Answer: Yes.

"Question: And it's from Kathryn Mallari to you; correct?

"Answer: That's correct.

"Question: And the subject of her e-mail is Periostat SLI 444, formulation development technical report. Correct?

"Answer: That's correct.

"Question: Okay. And your response is dated May 24th, 2000, at 4:36 in the afternoon. Correct?

"Answer: Correct.

"Question: And you wrote, Kathy, SLI 444 project is a straightforward program.

"You did write that?

"Answer: Yes.

"MR. SHULMAN: Let's mark for identification as Exhibit 21 a multi-page document bearing production numbers SUP 27412 through 417.

Now, do you see on page 1 of this document about, oh, a third of the way down the page, there is an e-mail from Kathryn Mallari, dated June 1, 2005, addressed to a number of different people, including Chris Powala and Klaus Theobald at CollaGenex; correct?

"Answer: Yes.

"Question: Okay. And the subject of Ms. Mallari's e-mail is Oracea CMC section/NDA question, responses and prep activities; correct?

"Answer: Correct.

"Question: And the e-mail that she wrote there was forwarded to you on June 1, 2005, at 1:50 in the afternoon. Correct?

"Answer: Yes.

"Question: Okay. And in the e-mail that was forwarded to you, Ms. Mallari wrote: Tara and CollaGenex, please see below. The Shire Labs' response to Tara's questions are indicated after each question.

"And then there is the heading, Tara's questions.

"Do you see that?

"Answer: Yes.

"Question: And Tara is from CollaGenex?

"Answer: I don't know.

"Question: Anyway, the first questions are,

one, how is the formulation selected? On what basis? What are the factors that led to the selection of the formulation selected? Is there any supporting development studies/ report that we can include here? We will need an approved report for the application.

"And then there is the answer, which says, with regard to formulation selection, this was based on CollaGenex's preferences after the review of PK studies data and in silico modeling of those results.

"And then it goes on with a couple more sentences.

"Do you see that?

"Answer: Yes.

"Question: Was it your understanding that with regard to formulation selection, the formulation was selected based upon CollaGenex's preferences after the review of PK studies data and in silico modeling of those results?

"Answer: Yeah. CollaGenex is the client. They have the final say in the formulation.

"Question: Dr. Chang, I just want to ask you a question about some testimony that -- that you testified about this afternoon.

"Mr. Shulman had asked you a question that said: In the Adderall product, what was the relative ratio in the

final product between the IR beads and the DR beads.

"And your response was: To answer your question, for Adderall XR, the IR and DR ratio is 1:1, but this is no comparison between the project because Adderall is and at the time -- oh, and is amphetamine. For this, the Periostat is doxycycline. The physical/chemical property is totally different, even the biopharmaceutical is different, so you cannot put together.

"Can you just explain for me what you meant?

"Answer: Every project have different thing. Project. Project.

"A different thing. For amphetamine at that time we looking for rising profile, so the -- the -- the second dose will -- many build up from the first -- first peak, so you can see the one peak build up, the other will be even higher. They don't have -- they don't create a plateau. Plateau, the plasma profile.

"The plateau plasma profile is bad for the ADHD patient. It will build up the tolerance.

"So that -- that's the thing will build up. That's the -- the marketing strategy, and those are the science based -- based development plan.

"For doxycycline is totally different thing. For doxycycline, we use the DR beads, try to minimize the -- get the -- the absorption difference between the upper G.I.

and lower G.I., so we -- we do need the DR beads, try to dissolve in the up -- the up -- in the small intestine quickly to pump out everything for -- pump out -- pump.

"Question: Pump out?

"Answer: Pump out everything from the DR beads in the small intestine to minimize the bioavailability loss. Bioavailability loss. And gain the -- the duration. So it is totally different."

(End of videotaped deposition.)

THE COURT: Is there another deposition?

MS. GILL: Another deposition.

Your Honor, Mylan would like to call the second named inventor on the Chang patents, Arash Raoufinia.

MS. WILLGOOS: Again, your Honor, we have an exhibit that's not included in Mylan's --

THE COURT: All right. Please pass it up.

MS. WILLGOOS: And plaintiffs would like to move for the admission of DTX-1074.

THE COURT: Any objection?

MS. GILL: No objection.

THE COURT: All right. It's admitted.

(DTX-1074 was admitted into evidence.)

(Videotaped deposition of Arash Raoufinia played as follows.)

"Question: Would you state your full name,

please.

"Answer: Arash Raoufinia.

"Question: And the degree is in what field, sir?

"Answer: Doctor of Pharmacy.

"Question: Okay. And it also says in the e-mail that the goal for Cmax was less than 750 nanograms per milliliter, plus or minus one standard deviation below one microgram per milliliter.

"Correct?

"Answer: Yes. That's -- that's what is stated.

"Question: Okay. So the Cmax and Cmin range that you see here is a range that was given to you by somebody else, not a range that you came up with yourself; is that correct?

"Answer: Definitely not by myself.

"Question: Was it the goal in this doxycycline project to obtain a -- a plasma profile at steady state that approximated the plasma profile at steady state that one gets from taking Periostat twice a day?

"Answer: Based on what I set as parameters, I think the -- the parameters are already set in the contract, and we have seen that in there.

"Question: Cmin and Cmax?

"Answer: Seems like we have already set those

parameters prior, in the -- in the prior exhibits.

"MR. SHULMAN: Let's mark for identification as Exhibit 12 SUP 31435 through 42.

"Is this a copy of an e-mail that you sent to Mr. Flanner and Dr. Chang on November 6th of 2002, attaching a copy of the in silicon doxy report?

"Answer: Yes.

"Question: Okay. And were you the one who prepared the report that's attached to this e-mail?

"Answer: Yes.

"Question: Now, let's mark as Exhibit No. 15 a document bearing production number SUP 36792 through 36800.

Okay. And its subject is a Perio -- Periostat XR preliminary in silico modeling report.

"Do you see that?

"Answer: Yes.

"Question: Okay. And it goes on to say that: The following preliminary report was forwarded to CollaGenex on November 14th of 2002. Do you see that?

"Answer: Yes.

"Question: Okay. Now, let's go to the first substantive page.

"And there on the first paragraph, you wrote that: CollaGenex requested Shire to conduct in silico modeling to evaluate feasibility of once-a-day dosing of

doxycycline monohydrate for an adjunct treatment of signs and symptoms associated with periodontitis in adults.

"Do you see that?

"Answer: Yes.

"Question: You did write that; right?

"Answer: Yes.

"Question: And we also saw earlier that the modeling efforts themselves began, I believe it was October 28th of 2002. Do you recall that? We can go back and look at the date, but it --

"Answer: Right. Yes. I recall as the official time to start the work, yes.

"Question: And the second photograph also states that: After reviewing the results of the PK study, CollaGenex requested Shire to conduct in silico modeling of different ratios of IR to DR beads in a single formulation to evaluate the possibility of once-a-day dosing of doxycycline. Do you see that?

"Answer: Yes.

"Question: And you did write that?

"Answer: Yes.

"Question: Okay. And, incidentally, when you were writing this report, did you try and be truthful and accurate to the best of your ability?

"Answer: Yes.

"Question: So let me ask you the question again. Is it correct that one of the purposes of performing the in silico modeling of these various IR to DR formulations was to predict the steady state in vivo plasma concentration profiles for each?

"Answer: Yes.

"Question: Now, as of November 14th, 2002, which is the date of this report, in Exhibit 15, had you done any in silico modeling of doxy formulations other than the six formulations that are described in this report?

"Answer: Yeah. This -- the model -- I usually do many different combinations, and I usually do many of them, and this report says that out of all the generated, these are the ones that are presented that shows within the profiles.

"Question: Within the profiles?

"Answer: Yes.

"Question: Okay. What did you mean when you wrote that CollaGenex and Shire will discuss which of the ratios in the report appears most promising from an IP standpoint?

"Answer: This is a very general term that I used, to talk about different angles, so ...

"Question: What does IP stand for?

"Answer: IP stand for intellectual property.

"Question: Okay. What did you mean when you wrote that CollaGenex and Shire will discuss which of the ratios appears most promising from an intellectual property standpoint?

"Answer: I didn't mean anything in terms of other than the fact that these are the -- the items that needs to be discussed prior to making a decision on the formulation.

"Question: Yes. Is it correct that in this report, Exhibit No. 15, there is no profile data concerning a 40 milligram doxy formulation where the ratio of IR to DR beads is 75/25?

"Answer: At what dose level?

"Question: At any dose level.

"Answer: Any dose level. This -- this report only shows 80/20 for the 40 milligram, and shows a 70/30 for the 45 milligram, yeah. So specifically 75/25 is not mentioned in this report.

"Question: Did you make the selection of the IR to DR bead ratio that should be used for further study?

"Answer: No, I did not.

"Question: Did you come up with the idea of a 75 to 25 ratio of IR beads to DR beads?

"Answer: I don't recall.

"Question: You don't recall having done so?

"Answer: I don't recall having done so, yes.

"Question: Okay. And then it goes on to say: Based on the modeling results, CollaGenex has requested that Shire prepare a pilot scale GMP supplies consisting of a 40 milligram doxycycline allocated as 75 percent in IR form and 25 percent in DR form in a single PR dosage unit and for evaluation in a human PK study.

"Do you see that?

"Answer: Yes.

"Question: Does that refresh your recollection that CollaGenex requested the 75/25 bead ratio?

"Answer: I wasn't really involved after the modeling, as I mentioned, with the decisions and the manufacturing steps.

"Question: Did you have any involvement in making a 75/25 composition as described here in Exhibit 17?

"Answer: I don't believe so. I don't recall.

"Question: Apart from this occasional participation in the -- in the manufacturing of the 75/25 formulation, did you have any further involvement in the 75/25 formulation?

"Answer: I don't recall having any involvement. Again, my -- my involvement finished mostly after the modeling part.

"Question: Okay. And did you believe that you

were a joint inventor of the subject matter claimed in the application at the time that you signed this declaration?

"Answer: Yes.

"Question: Were you the one who first thought of the idea of a once daily formulation of doxy that had 40 milligrams in it?

"Answer: Based on modeling, it seems -- seemed that the 40 milligram -- the 45 are possible options.

"Question: Right. But someone told you to model 40 milligrams and 45. It wasn't your idea; is that correct?

"Answer: I believe we discussed this at the beginning that this was the set of specifications provided to us.

"Question: By CollaGenex?

"Answer: I believe it was CollaGenex, yeah.

"Question: Okay. But once daily was the objective of the overall project that CollaGenex had contacted Shire for; right?

"Answer: Correct.

"Question: Okay. Among the three inventors, who was the person who first thought of such a formulation having a 3 to 1 ratio of IR to DR beads?

"Answer: I don't know who was the first person.

"Question: Do you know when that idea was first

formulated?

"Answer: No.

"Question: Among the three of you, who was the first person who -- who thought of -- who first thought of such a 3 to 1 formulation, where the immediate and delayed release portions are in the form of pellets?

"Answer: I don't know who was the first person.

"Question: Do you know if any of the three of you were the first person to think of that idea?

"Answer: I don't know.

"Question: Among the three of you, who was the first person who first thought of such a 3 to 1 formulation, where the delayed release pellets are coated with an enteric polymer?

"Answer: I don't know.

"Question: Was it you?

"Answer: No.

"Question: Among the three of you, were you the person who first thought of such a 3 to 1 pellet formulation that also included an excipient?

"Answer: I don't know.

"Question: It wasn't you?

"Answer: No.

"Question: Okay. Among the three of you, were you the first person who thought of such a 3 to 1 pellet

formulation where the pellets are contained in a capsule?

"Answer: I don't know.

"Question: It wasn't you?

"Answer: No.

"Question: And now if you go to claim 4, it modifies claim 1 so that the minimum steady state level is .3, and the maximum steady state level is .8 micrograms per milliliter; correct?

"Answer: Correct.

"Question: Were you the person who first thought of a once daily 40 milligram doxy formulation having a 3 to 1 ratio of IR to DR pellets that gives steady state blood levels of between .3 and .8 micrograms per milliliter?

"Answer: I wasn't the first one.

"Question: You were not?

"Answer: (Shaking head no.)

"Question: Okay. And according to figure 4, the steady state blood levels for doxy obtained from the once daily administration of 40 milligrams of immediate release doxy also fall between .1 and 1.0; correct?

"Answer: Yes, it does.

"Question: Now, let's look at figure 5. That figure shows steady state blood levels for the once daily 40 milligram dose of doxy that contains a 75 to 25 ratio of IR and DR beads; correct?

"Answer: Correct.

"Question: Is it correct that according to figure 5, the 75/25 dosage form results in some steady state blood levels that do not fall within the range of .3 to .8 micrograms per milliliter?

"Answer: They are all below .8 or 800, but some of the points are below 300.

"Question: Right. Is it correct that according to figure 5, the 75/25 formulation -- strike that.

Is it correct that in figure 5 for the 75/25 formulation, the minimum steady state blood level is about .16 micrograms per milliliter, which is less than .3?

"Answer: Yes.

"Question: Are you aware of any data in your patent which shows that from a once daily dosage of 40 milligrams of doxy, all of the blood levels achieved at steady state fall between a minimum of .3 and a maximum of .8 micrograms per milliliter?

"Answer: So you are referring to the patent, so I would like to look through the data.

"Question: Sure.

"Answer: There is no other data in the patent.

"Question: So is the answer to my question yes?

"Answer: Yes.

"Question: You are not aware of any data in the

patent which shows that from a once daily dosage of 40 milligrams of doxy, all of the blood levels achieved at steady state fall between a minimum of .3 and a maximum of .8 micrograms per milliliter; correct?

"Answer: That's correct.

"Question: Okay. At the time you were preparing to undertake the in silico modeling studies, did you believe that it was preferential to have at least 80 percent of the formulation in the form of an IR portion, and the rest in the form of a DR portion?

"Answer: No.

"Question: Okay.

"Answer: My -- my understanding was based on model predictions, so ...

"Question: At the time you were preparing to undertake the in silico modeling studies, did you believe that it was preferential to have more than 50 percent of the formulation in the form of an IR portion?

"Answer: That was not given prior to the modeling.

(Depositions designations end.)

MS. GILL: Your Honor, we would like to call the third and final inventor of the Chang patent, Niraj Shah.

THE COURT: Also by deposition?

MS. GILL: Also by deposition.

(Deposition of Niraj Shah played.)

"Question: Would you state your full name, please?

"Answer: Niraj Shah.

"Question: You can put your hand down.

"You can keep it up, too, if you'd like.

"What's your residence address?

"Answer: 2097 Misty Meadow Road, Finksburg, Maryland 21048.

"Question: Okay. And you joined Supernus or Shire Laboratories back in late September of 2001?

"Answer: Somewhere, correct.

"Question: And you were there until roughly September of 2005?

"Answer: I would say it's five or six. I could not recall.

"Question: Okay. Do you know whether someone at CollaGenex was the first person to conceive of the idea of developing a once daily formulation of doxycycline?

"Answer: I don't have any correct answer on this.

"Question: Did you have any responsibility for determining what ratio of IR to DR beadlets should be included in the doxy capsule product?

"Answer: No.

"Question: Did you have any responsibility for determining what amount of doxycycline should be included in each doxy capsule?

"Answer: No.

"Question: Did you have any responsibility for determining what range of steady state blood levels of doxycycline should be achieved by the capsule product?

"Answer: No.

"Question: Now, when you joined Shire, were there any existing technologies that you used to assist you with making the IR beads and the DR bead?

"Answer: No.

"Question: Apart from you and Dr. Chang, did anyone else participate in making the formulations for the IR and DR beads for the doxycycline project?

"Answer: Making was my responsibility. Interpreting and developing was my supervisor's responsibility. Apart from them, there was another guy named Arash Raoufinia was involved in that -- between when we are in the development stage.

"Question: Did there come a point in time when you learned that the focus of the doxy project would be directed to a capsule formulation containing IR and DR beads in a ratio of 75 to 25?

"Answer: I was not aware of, but I cannot make

any gauge or estimate, so basically I have no idea.

"Question: Okay. But you don't recall coming up with the idea that we ought to pursue 75/25?

"Answer: I don't recall.

"Question: What was the basis for your belief that you were an inventor of the subject matter claimed in this application?

"Answer: This is again, it's a group effort to work together on a project. Initially myself and Dr. Chang, we worked together to come out with the various formulation.

"Question: Um-hmm.

"Answer: And then Dr. Chang, with Dr. Raoufinia, applied those to the in silico modeling, and all the compilation of data made come to a conclusion that we have an invention, yes.

(Deposition designations end.)

MS. GILL: Your Honor, Mylan would like to call Padmanabh Bhatt by deposition. Mr. Bhatt was designated by Supernus as a 30(b)(6) witness.

THE COURT: Okay.

(Deposition of Padmanabh Bhatt played.)

"Question: Would you state your full name, please?

"Answer: Padmanabh Bhatt.

"Question: And by whom are you employed?

"Answer: Supernus Pharmaceuticals Inc.

"Question: And for how long have you been employed by Supernus?

"Answer: Since its formation. December 2005.

"Question: Okay. And were you employed by the predecessor company, Shire Labs?

"Answer: That's correct.

"Question: When did you join Shire Labs?

"Answer: January 2003.

"Question: Okay. Have you ever heard of something called Microtrol technology?

"Answer: Yes.

"Question: Does that refer to?

"Answer: Microtrol is a trademark term that was used and probably continues to be used by businesspeople to broadly describe the different concepts we have developed for beads in a capsule.

"Question: And what is the bead technology to which it refers?

"Answer: It doesn't refer to a technology, it refers to the general concept of having beads that will provide a certain type of profile that is custom developed, that's invented for different products for differing needs, and putting those beads in a capsule. So it's a very generic term that does not really focus on one idea.

"Question: Now, let's mark as Exhibit 9 another document bearing production numbers SUP 18 through 19.

And is this -- do you recognize this document?

"Answer: Yes.

"Question: And is this the second amendment to the development and license agreement that is Exhibit 7?

"Answer: Correct.

"Question: Have you ever heard of a product called Periostat?

"Answer: Yes.

"Question: And that's a twice-a-day formulation of 20 milligrams instant release doxycycline?

"Answer: That's correct.

"Question: Was it your understanding that the goal of the development project set by CollaGenex was to develop a once-a-day formulation that mimicked the blood profiles achieved from twice-a-day Periostat?

"Answer: My understanding is that Shire Labs was chartered to develop a doxycycline formulation that could be dosed once a day that would produce blood levels between .1 and 1 microgram per ML.

"Question: Do you know where CollaGenex got the .1 to 1 blood level range?

"Answer: You would have -- that would be up to CollaGenex to answer.

"Question: What is your understanding of where necessity obtained that range?

"Answer: SUP -- Shire Labs/Supernus' strategy was to accept the requirement, target requirement that the partner provided. And so we -- we accepted CollaGenex's direction in that regard.

"Question: Prior to the efforts that began at Shire in 2001 to work on this once-a-day formulation of doxy, had any third party worked on a once-a-day formulation of doxy, to your knowledge?

"Answer: I do know what others have testified to, but I have seen at least one document that refers to a company called Faulding.

"Question: Do you know what, if any, problem Faulding encountered in attempting to develop this product?

"Answer: I have seen data that shows that the bioavailability from 40 milligram once-a-day product was very low.

"MR. SHULMAN: Okay. Let's mark as Exhibit 12 a copy of Ashley's published U.S. publication, 2004/0115261.

"Question: Have you seen this document before, sir?

"Answer: I don't recall seeing it.

"Question: Once you took over responsibility for the patent affairs of the company, did you read the

Ashley application?

"Answer: No, I did not.

"Question: Would you look at paragraph 17, please, of the application.

"Answer: Yes.

"Question: Where they're talking about the blood levels of the tetracycline compound achieved from the use of the compound of the invention.

"Do you see that? Do you see that?

"Answer: Paragraph 17 says, amount of tetracycline compound, yes.

"Question: Okay. And the blood levels achieved from the compound of Mr. Ashley's invention is said to be between .1 and 1 micrograms per milliliter. Do you see that?

"Answer: Yes, I do.

"Question: And preferably between .3 and .8 micrograms per milliliter; correct?

"Answer: Correct.

"Question: And those are the same ranges that you all were instructed to work on at Shire; correct?

"Answer: Yes.

"Question: Okay. Now the -- the Oracea project -- product as well as the Chang patent claims called for 40 milligrams of doxycycline in the dosage form. Are

you aware of that?

"Answer: Yes.

"Question: Okay. Whose idea was it to include 40 milligrams in the dosage form?

"Answer: We carried our prototype development with various product concepts. CollaGenex would do a clinical study, we would receive the data back, and we would make recommendation to CollaGenex as to what we thought was the right approach to go forward with.

"CollaGenex would agree or disagree, and if they agreed, we would keep moving forward.

"MR. SHULMAN: Okay. Let me show you what we'll mark as Exhibit 13, I think. Thanks:

"Question: Which is a May 27, 2001 agreement between Shire and CollaGenex.

"Answer: Yes.

"Question: Bearing production numbers SUP 36372 through 383.

"You recognize this as a development agreement --

"Answer: Yes.

"Question: -- between Shire and CollaGenex?

"Answer: That's correct.

"Question: And it's dated May 22nd, 2001?

"Answer: Correct.

"Question: And in the background on the very first page, first paragraph, it says that: CollaGenex has requested that Shire conduct formulation development activities to evaluate the application of Shire's Microtrol technology with doxycycline hyclate as a line extension to Periostat for the indication of periodontitis.

"Do you see that?

"Answer: Mm-hmm. Yes.

"Question: To your knowledge, was that statement true?

"Answer: Yes.

"Question. And it goes on to say that: 'CollaGenex desires development of a controlled release oral solid dosage form that can deliver up to 40 milligrams of doxycycline, over a six to eight-hour period of time, in a dosage unit of reasonable size and appearance'?

"Answer: Correct.

"Question: Is that what CollaGenex wanted Shire to do, according to your understanding?

"Answer: The document says Shire was supposed to attempt to create a once-a-day formula -- create a formulation that can deliver 40 milligrams doxycycline over a six to eight-hour period.

"Question: Was Shire interested in developing a doxycycline once a day 40-milligram product before

CollaGenex approached it?

"Answer: Shire did not have an internal program to develop doxycycline --

"Question: Okay.

"Answer -- once a day.

"Question: And did Shire have any information about how much doxycycline should be contained in a once-a-day dose before CollaGenex informed it of the 40 milligrams?

"Answer: Well, Shire Laboratories would have seen the information that was available, either from CollaGenex or in the public domain, on the existing Periostat product.

"Question: Could you look at paragraph 49, please. And just read that to yourself.

"Answer: I've read it.

"Question: Okay. Do you see that it says: The tetracycline composition of the invention can be administered in the form of a liquid as a suspension or solution, or alternatively in solid form, such as a tablet, pellet, particle, capsule, or soft gel.

"Do you see that?

"Answer: I see it.

"Question: The formulation that was developed at Shire and formed the subject matter of the Chang patent

is a capsule; correct?

"Answer: That's correct.

"Question: Containing pellets; correct?

"Answer: That's correct.

"Question: And pellets are sometimes referred to as beadlets?

"Answer: Yes.

"Question: Okay. And the formulation that Shire developed that formed the subject matter of the Chang patent had a blood serum concentration level of .1 to 1; correct?

"Answer: That was the target, yes.

"Question: And that's what ultimately was claimed in the Chang patent; correct?

"Answer: Correct.

"Question: And you also claimed in the Chang patent a preferred blood level range of .3 to .8; correct?

"Answer: That's correct.

"Question: Okay. And you also claimed in the Chang patent a 40-milligram dosage form; correct?

"Feel free to look at the patent.

"Answer: Yeah, I can look at the patent.

Yes. Claim 1 of the Chang patent claims: An immediate release portion comprising a drug wherein the drug consists of about 30 milligrams doxycycline, and a delayed

release portion comprising a drug where in the drug consists of about ten-milligram of doxycycline.

"So if you add those two up, it adds up to 40.

"Question: Okay. Now, would you look, please, back at paragraph 49 of the Ashley application.

"Answer: Yes.

"Question: And it says, in the second sentence: For example, the form can be polymeric capsules filled with solid particles which can in turn be made to release the tetracycline compound according to a known pattern or profile. Such particles can also be made to have more than one release profile, so that over an extended time, the combined release patterns provide a pre-selected profile.

"In the doxycycline product that you developed at Shire and which formed the basis for the invention of the Chang patent, is it correct that you had two different particles in the capsule?

"Answer: That's correct.

"Question: And one of the particles in the product that you developed at Shire was an instant release particle?

"Answer: An immediate release particle, yes.

"Question: Or immediate release, yeah.

"And the other one was a delayed release particle?

"Answer: That's correct.

"Question: Okay. And is it correct that the instant release particle had a release profile that was different than the release profile obtained from the delayed release particle?

"Answer: The immediate release particle and the delays -- delayed release particle have different release profiles.

"Question: Is it correct that in the work that you did at Shire which led to the Chang patent, you combined the delayed release particles with the instant release particles to obtain a combined release profile that fit to a pre-selected target you were looking for?

"Answer: We created a profile that met the performance criteria.

"Question: And that's the .1 to 1?

"Answer: That's correct.

"Question: Okay. And you did so by combining the release profile obtained from the delayed release portion with the release profile obtained from the immediate release portion; correct?

"Answer: We combined the two beads, the immediate release bead and the delayed release bead, to create a -- a performance that met the -- the -- the performance criteria that were established for the product.

"Question: If you go to the description of figure 4 in column 3, it tells you that these graphs are for doxycycline; correct?

"Answer: It does.

"Question: Okay. So now let's go back to figure 4.

"Is it correct that the administration of 20 milligrams instant release doxycycline twice a day, as shown in figure 4, yields blood serum concentrations that fall between .1 and 1.0?

"Answer: That's correct.

"Question: Now let's look at the white squared graph in figure 4, which has the highest peak. Do you see that one?

"Answer: I do.

"Question: Okay. And that's for 40 milligrams instant release doxycycline taken once a day; correct?

"Answer: That's correct.

"Question: And the steady state blood levels concentration for that form of administration also fall between .1 and 1.0; correct?

"Answer: That's correct.

"Question: Now, if we could return to the Chang patent, please.

"Answer: Yes, sir.

"Question: So comparing the 40-milligram IR once-a-day formulation in figure 4 to the two IR/DR combinations in figure 4, is it correct that all three will, quote: 'Give steady state blood levels of doxycycline of a minimum of .1 micrograms per milliliter and a maximum of 1.0 micrograms per milliliter'?

"Answer: The profiles fall between .1 and 1, but you have to remember that these are mean average profiles, and the individual subjects may not fall, for example, if you take the 40-milligram IR and give it once a day, there -- there will -- there -- there will be more individuals sub -- subjects that may have excursions above the one microgram per ml level with an average still showing below one microgram per ml. So you -- you know, that does not meet, really, the -- the intent from a marketing perspective for the product --

"Question: Okay. And the -- I'm sorry. Go ahead.

"Answer: CollaGenex is trying to minimize the exposure of subjects to microbial or antibiotic levels of doxycycline. And by their definition, that cutoff point was one microgram per ml. So even though the mean profile for 40 milligram IR given once a day falls within that one microgram per ml cutoff point, the individuals may excurse (sic) above that, and that is not acceptable.

"Question: And the -- the same is also true with respect to individuals taking the DR or IR/DR formulations; correct?

"Answer: If -- if you are looking at the simulated profile at face value, you can see that the Cmax or the IR/DR combo is lower than the Cmax for the 40 milligram IR given once a day. And so the chances of individual subjects going above one microgram per ml from the IR/DR combo, the chances are less than for individuals who are exposed to the 40 milligram IR once a day.

"Question: But it depends on what the standard deviation is for each of these curves; correct?

"Answer: Yes.

"Question: Okay. Did Shire ever run standard deviations with respect to the 40 milligram IR once-a-day formulations that's referred to here in figure 4?

"Answer: I do not recall.

"Question: Okay. Can you tell from the data in figure 4 what the standard deviation is for any of these curves?

"Answer: No.

"Question: Okay."

(End of videotaped deposition.)

MS. GILL: Your Honor, we would like to move into admission DTX-2109.

THE COURT: Any objection?

MS. WILLGOOS: No objection, your Honor. We would like to move into evidence DTX-1074.

MS. GILL: No objection.

THE COURT: They're both admitted.

(DTX-2109 and DTX-1074 were received into evidence.)

MR. STEUER: Mylan rests.

THE COURT: All right. Is there a motion?

MR. FLATTMANN: Your Honor, yes. We move for judgment pursuant to Rule 502(c) of -- I'm sorry, your Honor. That Mylan has failed to meet its clear and convincing burden of proving the asserted claims to the three sets of patents invalid.

THE COURT: I'm going to take it under advisement, or is there a judgment, anything you wish to say at this point?

MR. STEUER: We many renew our previous motion.

THE COURT: Anything you wish to say?

MR. FLATTMANN: We oppose for the same reasons I stated a couple days ago, your Honor.

Your Honor, in terms of our rebuttal case, given the current state of evidence, we no longer intend to call life Dr. Oates or Dr. Murry, but we do have as part of our rebuttal case some limited deposition testimony that Ms.

Willgoos will introduce and a few housekeeping matters with relation to exhibits.

THE COURT: All right. And approximately how long would that deposition testimony run?

MS. WILLGOOS: About 20 minutes, your Honor.

THE COURT: About 20 minutes? All right. Well, we're going to take our afternoon recess and then we'll come back and allow you to do that.

For the record, I'm taking all the motions under advisement, reserving rulings on them until after trial.

We'll take a recess.

(Brief recess taken.)

THE COURT: You may proceed.

MS. WILGOOS: Thank you, your Honor. Plaintiffs would like to call by deposition designation, Jason Harper, one of Mylan's corporate witnesses. And pursuant to his testimony, we would like to move into evidence, DTX-2243.

MR. STEUER: No objection.

THE COURT: It's admitted.

(DTX-2243 received into evidence.)

MS. WILGOOS: May I approach the bench with the exhibit?

THE COURT: You may.

Let's turn down the lights.

(Deposition played of Jason Harper.)

"Question: Good morning, Mr. Harper.

"Answer: Good morning.

"Question: Okay. Let's mark this document bearing Bates numbers MYL-D 118531 through 540 as Harper Exhibit 4.

"Mr. Harper, have you seen these documents before?

"Answer: They are forecast documents for Mylan's generic version of Oracea.

"Question: Let's go back to the forecast in Exhibit 4 on page ending 540. I believe we started discussing earlier row 24, generic price index percent of brand.

Okay. So by -- by four months after Mylan's launch of its generic version of Oracea, generics are taking 85 percent of doses of Oracea in the market and branded Oracea has only 15 percent of doses; right?

"Answer: The assumption in C -- Q3 CY 12 is that 85 percent of the doses would be sold by the generics.

"Question: So let's just go to quarter ending December 2012. You got 90 percent generic substitution in that quarter; right?

"Answer: The assumption is 90 percent generic in Q4 CY 12.

"Question: And then the assumption in every

quarter from Q2 CY 13, through the end of this spreadsheet, Q1 CY 16, is that 95 percent of doses of Oracea will be generic doses and branded sales will make up only five percent of Oracea doses; right?

"Answer: The assumption from that point forward is 95 percent of the doses are generic and five percent are branded Oracea.

(Deposition designations end.)

MS. WILGOOS: We'd like to call our next witness, your Honor. We'll be hearing from Mr. Ashley one last time. Pursuant to that, we'd like to admit the DTX-1019.

MR. STEUER: No objection.

THE COURT: It's admitted.

(DTX-1019 received into evidence.)

MS. WILGOOS: May I pass up the exhibits?

THE COURT: You may.

(Deposition of Robert Ashley played.)

"Question: Good morning, Mr. Ashley. Could you please state your name for the record?

"Answer: Robert Ashley.

"Question: Okay. Let me mark as Ashley Exhibit No. 6 a document produced by plaintiffs in this action bearing Bates numbers GAL 224903 through 224928.

"Have you got what's been marked as Ashley

Exhibit 6 in front of you, sir?

"Answer: I do.

"Question: So April 1st, '00, which I presume is 2000, that's the date these individuals signed what's been marked as Ashley Exhibit 6?

"Answer: That's correct.

"Question: And you characterize this as the final protocol; is that right; sir?

"Answer: That's correct.

"Question: Now, let's mark for identification as Exhibit No. 2, Ashley Exhibit 2, a provisional patent application bearing production numbers MYL-DJ 2223 through 46.

"Okay. Now, when this application was converted to a non-provisional, you had to sign an oath and declaration; do you recall that?

"Answer: I don't recall signing --

"Well, I represent to you that's true, sir?

"Answer: I may have signed it. I don't recall.

"Question: And the oath and declaration, among other things, says that you read and understood the application, including the specification and the claims. Do you recall that?

"Answer: I don't recall having done that, but if I did, I did.

"Question: The question was, you stated in your declaration that you read and understood this paragraph that begins on page 11 at line 4; correct?

"Answer: What exactly does the declaration say?

"Question: I have read and understood the application, including the specification and claims.

"Answer: I don't recall having read this particular paragraph.

"Question: Well, you signed the declaration under penalty of perjury; correct?

"Answer: I have no idea whether -- I -- that's a legal phrase I don't understand.

"Question: Okay. Well I represent to you that you signed it under penalty of making false statements under oath. So ...

"Answer: Well, I have no idea whether the statement ...

"Question: So is it correct, sir, that you swore on your oath that you read and understood the paragraph that appears at lines 4 through 9 on page 11 of Exhibit 2?

"Answer: Well, I clearly signed that I'd read the patent, yes. I don't recall reading this particular statement. I don't necessarily understand what's meant by a delayed release agent in this context or generally. There

are, of course, all sorts of examples of delayed release agents, including, but not limited to, the ones that are here. So I probably read this paragraph -- or I read this paragraph, I had no reason to doubt its veracity, so I signed a statement to say that I'm sure it was true.

"Question: At the time you filed the application, did you have in mind any particular ratios or combinations of instant release, delayed release, and/or sustained release parallels that you thought would be useful to achieve a preselected release profile from a capsule?

"Answer: No.

"Question: When you filed your application, did you understand that you could select such a ratio, although you didn't know what ratio to select, to achieve a preselected release profile for a capsule formulation?

"Answer: I didn't know whether we could do that.

"Question: Okay. To your knowledge, sir, prior to 2001, was it known that one could achieve a preselected release profile for a capsule form of a drug composition by including in the capsule a ratio of instant release and delayed release particles containing the drug?

"Answer: I don't know specifically, no.

"Question: Were you aware of anyone who had done that?

"Answer: I was certainly aware of controlled release products. How they specifically achieved their objectives, I didn't know. I'd never been involved in the development of anything like that.

"Question: And is it your understanding that the information set forth in your application is insufficient to enable a formulator to make a once daily capsule tetracycline composition that will give steady state blood levels of between .1 and 1.0 micrograms per milliliter?

"Answer: Clearly, development work was required. I did not know what specific formulations would work, and I don't know whether an ordinarily skilled formulator would have been able to take this information. I don't know.

"Question: Prior to contacts with Shire, had CollaGenex attempted, either by itself or in conjunction with a third party, to develop a once daily dosage form of doxy?

"Answer: Yes, it had. Or it had attempted -- yes, it had.

"Question: On its own or with --

"Answer: No.

"Question: -- somebody?

"Answer: In conjunction with Faulding

Pharmaceuticals.

"Question: Okay. And do you recall that an objective of the program was to, as he reports here, develop a once-per-day dosage form that can meet bioequivalence criteria versus the current 20 milligrams twice-a-day dosage form?

"Answer: I don't recall the call. That's what Woody was reporting.

"Question: Okay. But do you recall -- even though you don't recall the call, do you recall that the objective of the program early on with Shire was to develop a once-per-day dosage form that can meet the bioequivalence criteria in comparison to the 20 milligrams twice-a-day dosage form?

"Answer: That certainly looks how Woody interpreted our objectives. I must admit, I don't recall having said that, but that's how Woody interpreted it.

"Question: And he also said that one of the objectives was given that the half-life of doxycycline is inherently 18 hours, the release profile would potentially only need to be four to eight hours. Do you see that?

"Answer: That, again, is what Woody has said in this document, yes.

"Question: Let's mark as Exhibit No. 4 a document bearing production numbers SUP 36372 through 83.

"Did CollaGenex ask Shire to formulate IR and DR beadlets for use in a capsule dosage form?

"Answer: I don't think so specifically. I mean, what happened was that over a period of time, a number of discussions took place where Shire proposed -- I mean, these idea -- we were -- CollaGenex was not a drug formulation company. CollaGenex didn't define any formulation. Shire would have defined any formulation that -- what we did was define the criteria we wanted the thing to end up with, which was this flat PK profile. CollaGenex didn't define anything.

"Question: Whose idea was it at CollaGenex to formulate a once daily controlled release oral solid dosage form that can deliver 40 milligrams of doxy as set forth in the first paragraph here?

"Answer: I'm not sure it was anybody at CollaGenex's idea specifically. Our idea was to flatten out the PK profile of doxycycline somehow. We had no idea how to go about that. Shire proposed one way of going about that -- and we had no idea whether it would work until we did it -- was to develop a controlled release oral solid dosage form. And there are other ways, of course.

"Question: Well, you had already been working on -- with Faulding on formulations, going back to the 90s, where you were trying to alter the PK profile; correct?

"Answer: And that had failed.

"Question: Do you know what rate and extent of release were specified by CollaGenex?

"Answer: And I don't recall.

"Question: Okay. But were those parameters specified by CollaGenex?

"Answer: I don't recall. I very much doubt it. I suspect that they would be specified by Shire. We specified what the outcome was that we wanted. I don't think we would have known necessarily what the rate and extent of release should have been to achieve that outcome, but I certainly don't recall defining those things. Again, CollaGenex is not a formulations company. CollaGenex is a -- was a drug development company, the clinical bit of it.

"Question: Okay. Now, in the conclusion of this report, it -- which is the last page, it states that the results obtained from the various IR and DR ratios at 40 and 45 milligram doses of doxy reveal that a once-a-day dosing may achieve the desired plasma profile. Do you see that?

"Answer: I see that statement.

"Question: Okay. What was the desired profile?

"Answer: I don't recall. Our clear objective was to remain well below the 1 microgram per mil top and to keep the area under the curve -- the total administered

available dose, if you like -- within a range which we believed would be effective. And I don't know whether -- and I don't recall how well we defined that, the bottom end, or whether we laid that out as a specific objective, but the top end was clearly an objective.

"Question: You mean the less than 1 microgram per ML?

"Answer: Right.

"Question: Okay. And you say the area under the curve was another criteria; correct?

"Answer: Right, as a measure of the total exposure of the patient, for want of a better word.

"Question: Okay. Over some period of time?

"Answer: Over a period of 24 hours at steady state.

"Question: Okay. And the experience that you had with respect to the effective amount of the drug over 24 hours as measured by AUC was based on Periostat; correct?

"Answer: Correct.

"Question: Okay. I think I understand. So in terms of the desired profiles, you had two objectives. One was to remain below 1.0 micrograms per milliliter, and, number two, try to approximate the AUC that you knew would work for Periostat if you could?

"Answer: Yeah, I'll go with what I said, was

that, you know, an ideal outcome would have been that we had no idea whether we could achieve an -- whether those things were mutually exclusive.

"Question: Okay.

"Answer: That was, of course, why we engaged Shire that had expertise in both formulation development and in the testing of those things. Our experience with Faulding suggested that those things were mutually exclusive.

"Question: Well, the record will reflect it. If now you want to say something, go ahead.

"Answer: Well, what I recall us doing with Faulding was something that I thought was really cleaver at the time, which was to try to alter the microenvironment in which the doxycycline was released by using organic acids, and I recall citric acid was one of them. It didn't work.

"Question: Okay. Do you recall any discussions about what ratio of IR to DR beads should be included in a pilot formulation?

"Answer: I recall Shire making recommendations to that effect --

"Question: What do you recall?

"Answer: -- following the PK data.

"I don't recall the numbers particularly. But there were clearly -- from their data -- from the data that

they'd obtained, there were clearly formulations which had a likelihood of success to achieve the objective, which we've talked about earlier, of maintaining the maximum, the Cmax, below this putative level and maintaining the AUC within a range which we thought would be effective.

"Question: I'd like to mark a document, and I'm just going to do it consecutively, as Ashley Exhibit 9.

"Do you recognize this document?

"Answer: I certainly recognize the consent tent. I'm not sure that I could say that I specifically recognize the document. But, yes, I do recognize the conversations we had with Faulding.

"Question: And so is this a document that Faulding prepared and sent to CollaGenex?

"Answer: It certainly looks like it -- yes, it is.

"Question: I'd like to mark as Ashley Exhibit 10 a document bearing Bates numbers SUP 0002421 through 0002445.

"And just for the record, because I forgot to state it, Ashley Exhibit 9 is Bates numbers SUP 0002414 through 2420.

"Just let me know when you have had a chance to take a quick look at Exhibit 10.

"Answer: Okay.

"Question: And is this a document sent by Faulding to CollaGenex with the subject matter of pilot blood study?

"Answer: Yes.

"Question: Okay. And do you understand that this is a summary of the pilot blood study that was conducted by Faulding or on Faulding's behalf?

"Answer: It certainly seems to be.

"Question: Okay. And I think you testified earlier that you considered the -- CollaGenex considered the Faulding formulations as failures; is that correct?

"Answer: Yes. I mean, it's fairly evident when you look at the graphs that maybe it delayed -- as mentioned in the cover letter, maybe uptake was delayed a little bit, but, you know, the overall absorption was -- I don't know -- 30 percent or something. The area under the curve was way too low.

"Question: Okay. So let's just take a step back for a second. Treatment A, B, C, and D, as set forth on page 2 of this document, do you understand that these were formulations that were tested in people, Faulding formulations that were tested in people?

"Answer: Yes. I guess that that's what these data -- the end data from individual subjects and then compiled data from all the subjects.

"Question: Okay. Did CollaGenex consider each of Treatments A, B and C as failures?

"Answer: Yes. There was nothing that even came close to the objective, and there were no stability problems.

"Question: What -- why did you consider these formulations failures?

"Answer: Because they didn't achieve what we believed would be an effective dose at a reasonably -- a reasonable administered dose."

(End of the videotaped deposition.)

MS. WILLGOOS: Just one last housekeeping matter, your Honor. We have some exhibits that were testified, were part of the testimony of Drs. Chambers and Gilchrest that we inadvertently did not move into evidence. We'd like to do so at this time, and documents for counsel and the Court, if you would like them.

THE COURT: Sure. Why don't you list them for us.

MS. WILLGOOS: Sure. PTX-199, PTX-200, PTX-201, PTX-202, PTX-208, PTX-209, PTX-470, PTX-492, and DTX-1640.

THE COURT: Any objection to any of those?

MR. STEUER: I don't anticipate an objection.

THE COURT: Take a look.

(Pause.)

MR. STEUER: No objection.

THE COURT: All right. They are all admitted.

(PTX-199, 200, 201, 202, 208, 209, 470, 492 and DTX-1640 were admitted into evidence.)

MS. WILLGOOS: Plaintiff rests, your Honor.

THE COURT: All right. Is there anything further from Mylan?

MR. STEUER: No surrebuttal.

THE COURT: All right. So where are we? You all have plenty of time left. My perception is you don't need it, but you do have the opportunity to do closings, and the request this morning was we put that off until tomorrow, which is fine. But I would like your estimates as to how much of your remaining time you anticipate using tomorrow.

MR. FLATTMANN: I would anticipate spending about one hour at most on the closing, your Honor.

All right. And Mylan?

MR. STEUER: Sounds about right.

THE COURT: All right. Will, let's meet tomorrow at 9:30, then. And you do have more than an hour each, but I think an hour is a very good target for both of you. Okay.

Anything else at this point?

MR. FLATTMANN: I believe that's all, your Honor.

THE COURT: No?

MR. STEUER: No, your Honor.

THE COURT: All right. Have a good night and we'll see you tomorrow at 9:30.

(Court recessed at 4:09 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s Brian P. Gaffigan
Official Court Reporter
U.S. District Court